

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS  
CORPORATION,

Plaintiff,

V.

LIQUIDIA TECHNOLOGIES, INC.,

Defendant.

Redacted - Public Version

C.A. No. 23-975-RGA-SRF

**DEFENDANT’S OPENING BRIEF IN SUPPORT OF ITS  
MOTION TO EXCLUDE THE OPINIONS AND TESTIMONY OF  
PLAINTIFF’S EXPERT DR. RONALD A. THISTED, PH.D.  
REGARDING INFRINGEMENT AND VALIDITY**

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Defendant Liquidia Technologies, Inc. (“Liquidia”) respectfully moves to exclude the opinions and testimony of Plaintiff United Therapeutics Corporation’s (“UTC’s”) expert, Dr. Ronald A. Thisted, Ph.D., regarding infringement and validity<sup>1</sup> because he admittedly does not meet the definition of a person of ordinary skill in the art (“POSA”) in this case, and therefore his identified opinions are inadmissible under Federal Rule of Evidence 702 (“Rule 702”).<sup>2</sup>

## **I. NATURE AND STAGE OF PROCEEDINGS**

This is a patent infringement litigation arising under the Hatch-Waxman Act and relates to the use of the drug treprostinil for pulmonary hypertension associated with interstitial lung disease (“PH-ILD”). D.I. 8, ¶¶ 1-3. The sole asserted patent is U.S. Patent No. 11,826,327 (“the ’327 patent”). *Id.*; D.I. 17. Fact and expert discovery are closed. D.I. 225, ¶ 4. This case is scheduled for a bench trial beginning on June 23, 2025. D.I. 45, ¶ 14. The pretrial conference is set for June 13, 2025. *Id.* at ¶ 12.

## **II. SUMMARY OF ARGUMENT**

1. Rule 702 sets forth three distinct restrictions on expert testimony—“qualification, reliability, and fit.” *Schneider ex rel. Est. of Schneider v. Fried*, 320 F.3d 396, 404-05 (3d Cir. 2003). “To offer expert testimony from the perspective of a skilled artisan in a patent case—like for claim construction, validity, or infringement—a witness must at least have ordinary skill in the art.” *Kyocera Senco Indus. Tools Inc. v. Int’l Trade Comm’n*, 22 F.4th 1369, 1376-78 (Fed. Cir. 2022); *see also Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363 (Fed. Cir. 2008)

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<sup>1</sup> The specific opinions of Dr. Thisted that should be excluded include the subject matter of the highlighted paragraphs, and portions of paragraphs, identified in Exhibit 1 (Thisted Rebuttal Report) and Exhibit 2 (Thisted Reply Report), both attached hereto.

<sup>2</sup> To the extent the Court does not view these issues as appropriate for a *Daubert* motion, Liquidia requests that the Court consider these issues as if in a motion *in limine* and exclude Dr. Thisted’s opinions and testimony regarding infringement and validity under Federal Rules of Evidence 402 (“Rule 402”) and/or 403 (“Rule 403”). *See infra* § IV.D.

("[W]here an issue calls for consideration of evidence from the perspective of one of ordinary skill in the art, it is contradictory to Rule 702 to allow a witness to testify on the issue who is not qualified as a technical expert in that art.").

2. Rule 402 provides that irrelevant evidence is not admissible. Rule 403 provides that the Court may exclude relevant evidence if its probative value is substantially outweighed by a danger of, *inter alia*, unfair prejudice, confusing the issues, or wasting time.

3. Dr. Thisted, by his own admission, is not a POSA in this case because he has no medical degree and no experience treating patients, let alone PH-ILD patients. However, his expert reports opine extensively regarding whether the claims of the '327 patent are valid and/or infringed when viewed from the perspective of a POSA. Because he is not a POSA, this testimony amounts to sheer speculation and is "neither relevant nor reliable" under Rule 702. *Kyocera*, 22 F.4th at 1377. Further, Dr. Thisted's identified testimony is irrelevant under Rule 402, and any potential relevance is substantially outweighed by the threat of unfair prejudice to Liquidia, confusing the issues, and wasting time under Rule 403.

4. Accordingly, Dr. Thisted's opinions regarding infringement and validity offered from the POSA's perspective, including at least those identified in Exhibits 1 and 2 attached hereto, should be excluded under Rule 702 or, alternatively, Rules 402 and/or 403.

### **III. STATEMENT OF FACTS**

#### **A. The '327 Patent and the Asserted Claims**

The asserted '327 patent claims methods of improving exercise capacity in PH-ILD patients by administering treprostinil by inhalation. D.I. 8-2 ("'327 patent"), 54:5-55:9 (cls. 1-19). PH-ILD is one of several different forms of pulmonary hypertension ("PH"), a progressive, life-threatening disease characterized by elevated blood pressure in lung vasculature. D.I. 54, ¶¶ 27-35. Specifically, PH is categorized into five groups by the World Health Organization ("WHO"),

and PH-ILD falls within WHO Group 3—PH associated with lung diseases and/or hypoxia. *Id.* PH-ILD is one of the most common diseases associated with Group 3, with PH reported in up to 86% of patients with interstitial lung disease (“ILD”). ’327 patent, 27:16-22. As noted in the ’327 patent, ILD is a “group of lung diseases.” *Id.* at 1:20-28, 2:53-67, 12:49-62, 29:1-30 (Table 4).

UTC asserts that Liquidia’s Yutrepia™ product infringes claims 1-11 and 14-19 of the ’327 Patent (“the Asserted Claims”). *See* Ex. 2, ¶ 2. Independent claim 1 recites:

A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration even that comprises at last 6 micrograms per breath.

’327 patent, 54:6-14. The remaining Asserted Claims all depend from claim 1 and recite, for example, methods wherein the claimed administration increases, reduces, or otherwise improves various clinical endpoints, when measured, such as the 6 minute walk distance (“6MWD”), plasma concentration of NT-proBNP, exacerbations of ILD, clinical worsening events due to ILD, or forced vital capacity (FVC). *Id.* at 54:5-55:9 (cls. 1-19); *e.g., id.* at 54:15-54:49 (cls. 2-10).

## B. Dr. Thisted is Not a POSA

In this case, the parties proposed the following definitions for a POSA for purposes of evaluating the alleged infringement and validity of the ’327 patent:

UTC’s POSA Definition	Liquidia’s POSA Definition
The POSA would have a graduate degree in medicine or a field relating to drug development, such as an M.D. or Ph.D., with <b><i>at least two years’ experience treating patients with interstitial lung disease, including with PH-ILD.</i></b>	A [POSA] would have a medical degree with a specialty in pulmonology or cardiology, plus <b><i>at least two years of experience treating patients with PH as an attending, including PH-ILD</i></b> and including inhaled therapies, or equivalent degree or experience.

D.I. 123, 4 (emphasis added); Ex. 1, ¶ 32; *see also id.* at ¶ 29 (“I understand that the validity of a patent is to be assessed from the perspective of a hypothetical [POSA] as of the effective filing

date.”); *id.* at ¶ 47 (“I further understand that the scope and content of the prior art must be viewed through the perspective of a POSA at the time of the invention.”); Ex. 2, ¶ 19 (“Counsel have advised me that patent infringement is evaluated from the perspective of a hypothetical [POSA].”). As shown, the parties agree that the POSA would have at least two years of experience treating patients with PH, including PH-ILD. *Id.*

During expert discovery, UTC submitted six reports in total from three technical experts regarding the alleged infringement and/or validity of the ’327 patent—(1) an Opening, Rebuttal, and Reply Report from Dr. Steven D. Nathan, M.D., (2) a Rebuttal Report from Dr. Bradley M. Wertheim, M.D., and (3) a Rebuttal and Reply Report from Dr. Ronald A. Thisted, Ph.D. Drs. Nathan and Wertheim are both board-certified pulmonologists with active clinical practices treating patients with pulmonary hypertension, including PH-ILD. D.I. 28, ¶¶ 4-14; Ex. 3, ¶¶ 5-9. Dr. Thisted, by contrast, is a biostatistician with no medical degree, and no experience treating patients, let alone those with PH-ILD. Ex. 1, ¶¶ 6-19. He therefore does not qualify as a POSA under the plain language of either party’s definition. *See* D.I. 123, 4.

In his Reports, Dr. Thisted never contends that he is a POSA, but instead asserts that he has “worked alongside and advised physicians who met the level of skill of the POSA under either party’s definition for various diseases” and that he is “familiar with the perspective of a POSA in this case, particularly as it relates to how a POSA would analyze and understand clinical data.” Ex. 1, ¶ 33; *see also* Ex. 2, ¶ 19. Based on this, he purports that he is “able to provide opinions reflecting the perspective of a hypothetical POSA under either party’s definition.” Ex. 1, ¶ 33. In his Rebuttal Report, Dr. Thisted states that he “reviewed a public, redacted version of a declaration of Dr. Nathan to learn about pulmonary hypertension, varieties thereof, and treatment options.” *Id.* at ¶ 59. Dr. Thisted’s Reply Report states that he reviewed Dr. Nathan’s Opening Report

regarding infringement, but he does not indicate he is relying upon Dr. Nathan's infringement analysis regarding independent claim 1.<sup>3</sup> Ex. 2 at ¶¶ 3, 8.

Dr. Thisted admitted in deposition that he is not a POSA for purposes of this case:

Q. You do not personally qualify as a POSA under UTC's definition, correct?

A. *Although I don't have a medical degree and I don't treat PH-ILD patients*, I have expertise that overlaps with what a POSA would have as relates to issues such as biostatistics, study design, analysis of studies, and evaluation of what they do and do not say, which would be part of -- which would be within the scope of what a POSA would have to have in order to review these patents.

Q. You do not have an MD, correct?

A. I do not.

Q. You do not have any experience treating patients with interstitial lung disease, correct?

A. That's correct.

Q. Let alone patients with PH-ILD?

A. Correct.

Ex. 4, 23:9-25 (emphasis added).

Further, Dr. Thisted's view appears to be that he meets some, but not all, of the qualifications of the parties' respective POSA definitions, further confirming that he makes no claim to actually be a POSA, or to possess the skills and experience that provide a POSA with the relevant perspective for the '327 patent:

Q. [. . .] So your testimony is that you have some expertise that is relevant to the expertise a POSA would have, but you do agree with me that you don't meet the definition of a POSA that is recited here, correct?

[. . .]

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<sup>3</sup> Dr. Thisted summarily states that he "agrees with" Dr. Nathan's infringement analysis regarding dependent claims 11, 14, 15, and 16 but fails to explain why. Ex. 2, ¶¶ 323, 325, 327, 329.

- A. *I do not possess all of the qualifications that are enumerated in these two statements*, but I do have expertise that falls within the scope of what a POSA would have, *I just don't have all of that expertise*.

Ex. 4, 24:20-25:5 (emphasis added) (“two statements” referring to the parties’ two POSA definitions). Additionally, Dr. Thisted admitted that he did not speak with, or rely on any conversations with, Dr. Nathan or Dr. Wertheim when preparing his opinions. *Id.* at 16:1-15, 28:10-14. As a result, not only is Dr. Thisted unable to offer an opinion as a POSA, but he did not check with POSAs who were available to him to see if the opinions he offered would be viewed as correct by a POSA.

**C. Dr. Thisted Opines that a POSA Would Consider the '327 Patent Claims Valid and Infringed**

Despite not qualifying as a POSA, Dr. Thisted’s Rebuttal Report regarding validity and Reply Report regarding infringement both purport to present opinions from the perspective of a POSA (*i.e.*, a clinician with experience treating patients). For example, Dr. Thisted’s Rebuttal Report provides opinions “regarding how *the POSA* would evaluate and view the data disclosed” in the prior art references “and the appropriate conclusions, if any, that can be drawn from the data.” Ex. 1, ¶ 118 (emphasis added). As another example, he goes so far as to speculate which patients had a PH-ILD diagnosis in the prior art patient population, and asserts that a POSA would consider that population to be “unrepresentative” of PH-ILD patients. *E.g., id.* at ¶¶ 160, 189, 194, 273; *see also id.* at ¶¶ 138-140, 145, 172, 176, 180, 195-197, 201, 221, 232, 237, 245, 247, 250, 258. Indeed, Dr. Thisted asserts that the opinions of Liquidia’s expert, Dr. Channick—who is without question a POSA—were “based on a severe misunderstanding” of “what the prior art can demonstrate *to a POSA*.” *Id.*, ¶ 320 (emphasis added).

Dr. Thisted’s Reply Report impermissibly interprets, for example, how a POSA would understand the Asserted Claims, Liquidia’s Yutrepia<sup>TM</sup> label, and/or the INCREASE study results

cited therein. *E.g.*, Ex. 2, ¶¶ 223, 228-229, 235-236, 239, 242, 249-254, 275-277, 285-287, 309. And similar to his Rebuttal Report, Dr. Thisted’s Reply Report includes improper opinions evaluating the patient populations in the prior art. *E.g.*, Ex. 2, ¶ 202 (“Further, Faria-Urbina does not disclose methods targeting PH-ILD patients. Rather, Faria-Urbina 2018 concerns Group 3 PH and follows a heterogenous population of patients that were retrospectively selected and that include PH-COPD subjects. ***This is a different patient population*** than the one targeted by Yutrepia’s PH-ILD indication. . . .”) (internal citations omitted) (emphasis added); *see also id.* at ¶¶ 191, 194, 195, 198-200, 203-209.

As noted, Exhibits 1 and 2 attached hereto specifically identify, with highlighting, the improper opinions contained in the following exemplary paragraphs from Dr. Thisted’s Rebuttal Report and Reply Report, respectively, where he purports to opine from the perspective of a POSA:

	Paragraphs Containing Improper Opinion(s)
Thisted Rebuttal (Ex. 1)	¶¶ 3, 24, 83-84, 88, 118-120, 122-123, 125, 130, 132, 138-140, 142-143, 145, 156-161, 164, 172-173, 176-177, 180, 189, 194-197, 199, 201, 210-211, 216, 221-223, 226, 229-230, 232-234, 237-240, 245, 247-248, 250, 254, 258, 264-265, 267-320
Thisted Reply (Ex. 2)	¶¶ 3, 10-17, 107, 110-112, 179, 186-187, 189, 190-191, 193-195, 198-200, 202-209, 213-219, 221, 223, 226-334

Below are non-exhaustive examples of Dr. Thisted’s improper, wholly speculative opinions regarding how a POSA would assess the validity or infringement of the Asserted Claims:

- “Dr. Channick’s conclusions concerning what the prior art teaches are based on a ***severe misunderstanding*** of clinical study design that ignores fundamental limitations to ***what the prior art can demonstrate to a POSA. Based on the POSA’s medical education and training the POSA would understand that these limitations prevent the hindsight driven conclusions that Dr. Channick reaches.***” Ex. 1, ¶ 320.<sup>4</sup>
- “Faria-Urbina 2018, Agarwal 2015, Saggar 2014, and Parikh 2016 would not have demonstrated ***to prescribing physicians*** as of the priority date that inhaled treprostinil improves exercise capacity in patients with PH-ILD.” *Id.*

<sup>4</sup> For the bulleted citations, emphasis is added to all and internal citations are omitted from all.

- “The examples of the ’793 patent specification contain only aggregated data for pulmonary hypertension patients with various disease etiologies, and *a POSA would not understand from such disclosures any specific treatment effect for patients with a pulmonary fibrosis disease etiology.*” *Id.* at ¶ 125.
- “Moreover, the 15-patient cohort *appears to represent a very select subset of PH-ILD patients*, in that all participants had to have been referred to UCLA’s tertiary site for lung transplantation evaluation. I note that the criteria for referral are not described and could well vary from patient to patient. Consequently, at least for these reasons, *it is unclear how the data reported by Saggar 2014 would apply to the broader population of PH-ILD patients.* [] Additionally, the patients studied in Saggar 2014 were required to have ‘advanced’ pulmonary hypertension ( $mPAP \geq 35$  mm Hg;  $PAWP \leq 15$  mm Hg; and  $PVR > 240$  dyn s/cm). *I understand that PH-ILD patients with  $mPAP \geq 35$  mmHg is only a subset of all PH-ILD patients:* [graph].” *Id.* at ¶¶ 138-139 (discussing prior art reference Saggar 2014).
- “As noted above, only 21 patients had data on change in 6MWD, an unknown number of which had PH-ILD. *Assuming that the PH-CPFE patients count as PH-ILD*, we can only conclude that the number of PH-ILD patients for which 6MWD changes are reported is between 6 and 20, either limit being a very small sample size.” *Id.* at ¶ 176 (discussing prior art reference Agarwal 2015).
- “This small patient cohort is also *likely to be unrepresentative of PH-ILD patients* due to the study’s PVD inclusion criteria (i.e., the hemodynamic requirements), *which generally required severe PH* or an indication that pulmonary vascular disease was ‘the predominant physiopathologic mechanism for PH.’” *Id.* at ¶ 194 (discussing prior art reference Faria-Urbina 2018).
- “Additionally, Dr. Channick mischaracterizes the results that Parikh 2016 reported. First, Parikh 2016 did not find (or report) that PH-ILD patients showed an improvement in the 6MWD. Instead, *patients diagnosed with PH-ILD were probably among the collection of the patients with PH of a wide variety of etiologies* (WHO Groups 1–5) for whom, in aggregate, increased 6MWD was observed.” *Id.* at ¶ 230.
- “. . . The article suggests that whether to perform the 6MWD assessment was based on the treating *physicians’ judgments* for each patient. A *physician’s judgment* that a patient’s condition was too severe to safely and successfully perform or complete the 6MWD test *could be one reason* for not performing the test; *such a reason would tend to remove patients who could not or would not perform well from the set of patients analyzed*, thereby introducing this bias along with others into the reported 6MWD change scores.” *Id.* at ¶ 196 (discussing prior art reference Faria-Urbina 2018); *see also id.* at ¶ 248.
- “*The POSA would not have had a reasonable expectation of success* in arriving at the claimed methods. *There was no expectation of success* that the clinical trial required to demonstrate an inhaled treprostinil treatment effect with respect to improved exercise capacity or any of the other claimed outcomes. Agarwal 2015, *which a POSA would recognize a [sic] merely an abstract*, concludes ‘[a] prospective trial is indicated.’ *A POSA*

would know or be informed that this step does not come with a reasonable expectation of success. Moreover, a POSA would not be buoyed by the '793 patent—a patent that does not address exercise capacity (or any other claimed outcome) at all and for which any PH-ILD data is masked amongst data reported in aggregate. A POSA would also understand that the '793 patent only reflects data from one dose administered during a right heart catheter. Therefore, a POSA would find no guidance relevant or otherwise in the '793 patent.” *Id.* at ¶ 311.

- “Dr. Channick asserts that a ‘POSA reading [the INCREASE] publication would not make the leap that Yutrepia™ administration would result in the same NT-proBNP levels.’ *I disagree that a POSA’s reading would be so limited. Rather, a POSA would apply the findings from the INCREASE study relating to NT-proBNP plasma concentrations to PH-ILD patients administered Yutrepia consistent with Yutrepia’s tentatively approved label.*” Ex. 2, ¶ 270.
- “. . . It is Dr. Channick who is improperly overlooking key information available to the POSA and that is also embedded and explicitly referenced in the Yutrepia label—the INCREASE study. Accordingly, I disagree with Dr. Channick’s personal opinion ‘that direct infringement of these claims requires a healthcare provider or patient to actively measure whether Yutrepia™ administration produces the claimed statistically significant outcomes.’ *But the claims do not require this*, and regardless it is unnecessary with respect to Yutrepia in view of the INCREASE study and especially in view of the tentatively approved Yutrepia label. *This is also why Dr. Channick’s position regarding what the ‘POSA would understand’ is wrong. The POSA would at least have Yutrepia’s label and the INCREASE study information and data cited therein*, and thus not need to ‘prescribe inhaled treprostinil (apply the intervention)[] to multiple patients (a group large enough to detect a meaningful difference), measure one of the selected parameters in each group member, aggregate the results from the patients, and then perform statistical analysis on those results.’ Instead, the treatment course need only be undertaken in accordance with Yutrepia’s label.” *Id.* at ¶ 235.
- “It is my opinion that administering Yutrepia according to Yutrepia’s tentatively approved label *will infringe* claim 9 of the '327 patent. Yutrepia’s tentatively approved labeling relies on reported methods of administering inhaled treprostinil to PH-ILD patients that achieve statistically significant treatment effects with respect to % predicted FVC after 8 weeks and 16 weeks as well as a statistically significant improvement in absolute FVC *in the IIP and IPF subpopulations* after 16 weeks as claimed. Accordingly, *it is more likely than not that PH-ILD patients, especially those within the IIP and IPF subpopulations*, administered Yutrepia consistent with its tentatively approved label will experience an inhaled treprostinil treatment effect with respect to % predicted FVC after 8 weeks and 16 weeks as well as a statistically significant improvement in absolute FVC *in the IIP and IPF subpopulations* after 16 weeks that were reported by the INCREASE study or its post hoc analyses.” *Id.* at ¶ 309.

By opining about what he imagines a POSA’s expectations and understandings would be, as well asserting that Liquidia’s experts “misunderstand” how a POSA would read the prior art and

the Yutrepia label, Dr. Thisted exceeds the scope of his expertise as a biostatistician and offers inadmissible opinions that do not pass muster under the *Daubert* standard.

#### IV. ARGUMENT

A witness must at least be a POSA to provide expert testimony on patent infringement or validity, and Dr. Thisted has admitted that he is not a POSA in this case. The result here is thus straightforward—Dr. Thisted’s opinions regarding validity and infringement of the Asserted Claims must be excluded under Rule 702.

##### A. Legal Standards

Rule 702, which codified the principles of *Daubert v. Merrell Dow Pharms, Inc.*, 509 U.S. 579 (1993) and its progeny, only permits expert testimony if it is more likely than not that:

- (a) the expert’s scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
- (b) the testimony is based on sufficient facts or data;
- (c) the testimony is the product of reliable principles and methods; and
- (d) the expert’s opinion reflects a reliable application of the principles and methods to the facts of the case.

Fed. R. Evid. 702 (amended Dec. 1, 2023). The Third Circuit has explained that Rule 702 “embodies a trilogy of restrictions on expert testimony: qualification, reliability and fit.” *Schneider*, 320 F.3d at 404-05. Qualification refers to the requirement that the witness possess “specialized expertise” in the pertinent subject matter. *Id.* at 404. Reliability means that the testimony “must be based on the methods and procedures of science rather than on **subjective belief or unsupported speculation**[.]” *Id.* (internal quotations and citations omitted) (emphasis added). Lastly, the expert testimony must “fit” the issues in the case, meaning that “the expert’s testimony must be relevant for the purposes of the case and must assist the trier of fact.” *Id.* “Rule 702’s ‘helpfulness’ standard requires a valid scientific connection to the pertinent inquiry as a precondition to admissibility.” *Daubert*, 509 U.S. at 591-92. The party offering expert testimony

bears the burden of proving admissibility. *Id.* at 592 n.10.

The validity and infringement of a patent must be assessed from the perspective of a POSA. *See, e.g., Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985); *see also Sundance*, 550 F.3d at 1364 (“Nor may a witness not qualified in the pertinent art testify as an expert on obviousness, or any of the underlying technical questions, such as . . . the scope and content of prior art, the differences between the claimed invention and the prior art, or the motivation of one of ordinary skill in the art to combine these references to achieve the claimed invention.”).

Federal Circuit law is clear that “[t]o offer expert testimony from the perspective of a skilled artisan in a patent case—like for claim construction, validity, or infringement—a witness must at least have ordinary skill in the art.” *Kyocera*, 22 F.4th at 1376-78 (finding that the district court abused its discretion in admitting an expert’s testimony regarding “any issue that is analyzed through the lens of an ordinarily skilled artisan[,]” where the “level of ordinary skill in the art . . . requires experience in power nailer design” and the expert, while having “advanced degrees in engineering and extensive experience in the design and manufacture of fastener driving tools[,]” “lack[ed] experience in power nailer design”); *see also Sierra Wireless, ULC v. Sisvel S.p.A.*, 130 F.4th 1019, 1024-25 (Fed. Cir. 2025) (finding abuse of discretion for relying on testimony regarding validity from expert who “does not satisfy the requirements for an ordinarily skilled artisan”); *see also HVLPO2, LLC v. Oxygen Frog, LLC*, 949 F.3d 685, 688-89 (Fed. Cir. 2020) (internal quotation and citation omitted) (“[I]t is an abuse of discretion to permit a witness to testify as an expert on the issues of noninfringement or invalidity unless that witness is qualified as an expert in the pertinent art. The prohibition of unqualified witness testimony extends to the ultimate conclusions of infringement and validity as well as to the underlying technical questions.”). The

opinions of an expert who lacks ordinary skill are “neither relevant nor reliable” and “not [] based on any specialized knowledge, training, or experience that would be helpful to the fact-finder.” *Kyocera*, 22 F.4th at 1376-77. Indeed, admitting expert testimony from a non-POSA ““serves only to cause mischief and confuse the factfinder.”” *Id.* (quoting *Sundance*, 550 F.3d at 1362).

Applying *Kyocera*, this Court and courts in this Circuit routinely exclude opinions from experts who do not qualify as a POSA. *See, e.g., Bausch & Lomb Inc. v. SBH Holdings LLC*, C.A. No. 20-1463-GBW-CJB, 2025 WL 591318, at \*2-6 (D. Del. Feb. 24, 2025) (excluding testimony regarding infringement from expert who was not a POSA); *Bial-Portela & CA. S.A. v. Alkem Lab’ys Ltd.*, C.A. No. 18-304-CFC-CJB, 2022 WL 4244989, at \*6-7 (D. Del. Sept. 15, 2022) (excluding testimony of two experts regarding their ultimate conclusions of validity and underlying technical questions because they did not meet the POSA definition); *Heron Therapeutics, Inc. v. Fresenius Kabi USA, LLC*, C.A. No. 22-985-WCB, 2024 U.S. Dist. LEXIS 87435, at \*8-10 (D. Del. May 15, 2024) (excluding expert opinions relating to a POSA’s expectations when the expert was not a POSA); *Takeda Pharm. Co. Ltd. v. Norwich Pharms., Inc.*, No. 20-8966 (SRC), 2022 WL 17959811, at \*33-34 (D.N.J. Dec. 27, 2022) (finding that “it is proper to exclude” the expert’s testimony on any “salt-related topic” where expert opined that a POSA would routinely perform a salt screen, while admitting that he had never performed a salt screen and thus “does not meet his own definition of a POSA.”), *aff’d*, 2023 WL 3244022 (Fed. Cir. May 4, 2023).

**B. Dr. Thisted’s Opinions regarding Validity Should be Excluded**

In his Rebuttal Report, Dr. Thisted opines extensively regarding whether a POSA would consider the Asserted Claims of the ’327 patent to be anticipated and/or obvious in view of the prior art’s disclosures. *See generally* Ex. 1; *see supra* § III.B. However, as Dr. Thisted himself acknowledges, the issue of patent validity must be assessed from the perspective of a POSA—

which he repeatedly admitted he is not. *Id.* at ¶¶ 29-33, 35, 47; Ex. 4, 23:9-25:10 (Dr. Thisted admitting he is not a POSA). The parties in this case agree that the POSA must have at least two years of experience treating patients with PH-ILD, and Dr. Thisted is a biostatistician with *zero* experience treating patients, much less those with PH-ILD. *See supra* § III.B.

Yet this does not stop Dr. Thisted from speculating about how a POSA would interpret the scope and content of the prior art and, ultimately, reaching the conclusion as to whether a POSA would consider the Asserted Claims to be valid in view of the prior art disclosures. His Rebuttal Report is replete with opinions regarding what a “POSA” would “understand” and/or “expect[]” based on the claim language and/or prior art at the time of invention, leading to his conclusion that the Asserted Claims are valid. *E.g.*, Ex. 1, ¶¶ 125, 211, 222, 254, 268-269, 273, 284, 286-288, 290, 295, 297, 299-300, 302, 311, 315, 317-318, 320. As one example, Dr. Thisted postulates that “a POSA would not have a reasonable expectation of success in arriving at the claimed methods” based on two prior art references “at least because a POSA would not expect treprostinil to have a treatment effect with respect to interstitial lung disease[,]” which “a POSA would understand” claims 7-8 to require. *Id.* at ¶ 297. Such opinions are pure conjecture, not based on any of Dr. Thisted’s own expertise, and are therefore irrelevant and unreliable under Rule 702. *Kyocera*, 22 F.4th at 1376-77.

Dr. Thisted stretches even further beyond his expertise by opining about patients’ PH-ILD diagnoses, and whether the prior art references’ patient populations were “representative” of PH-ILD. *See supra* § III.B; *e.g.*, Ex. 1, ¶ 197 (“Moreover, these conclusions are necessarily limited to the patient population to which the [prior art] chart review was directed: a highly screened sample cohort arrived at by applying inclusion criteria indicating severe PH and/or pulmonary vascular remodeling and exclusion criteria that appear to have excluded higher risk patients.”). For

example, when discussing the prior art reference Faria-Urbina 2018, Dr. Thisted opines that the study's "exclusions eliminated at least 27 [sic; 26] *patients who would be expected to have worse functional outcomes* than the 22 followed patients who did not meet those [exclusion] criteria." Ex. 1, ¶ 250 (emphasis added). During deposition, Dr. Thisted conceded that this opinion is merely speculation, as it must be since Dr. Thisted entirely lacks the necessary clinical expertise to form any such expectation. Ex. 4, 86:12-88:9; *id.* at 87:5-6 ("I suppose you could say it is a speculation . . ."). Dr. Thisted even goes as far as to disagree with the clinical conclusions in the Agarwal 2015 and Faria-Urbina 2018 prior art references, which were authored by undisputed POSAs in the PH-ILD field, such as Dr. Waxman:

Q. You don't dispute, of course, the express[] teachings of Agarwal, the paper does say that, correct?

A. It says that -- the paper -- I have accurately quoted and you have accurately stated back to me what the paper says in the conclusion.

The -- I would dispute the fact that the data in the paper indicate that treprostinil is effective. When they talk about effectively treating they don't say specifically effectively treating for other purposes.

Q. And so that is my next question. Your opinion is that you disagree with the authors' efficacy conclusion, correct? That is what you wrote in Paragraph 178.

[...]

A. Yes, I disagree with the authors' efficacy.

Q. And the authors of Agarwal include Dr. Waxman, correct?

A. He is the only other author besides Agarwal.

Q. And he is an expert in PH-ILD, correct?

A. Yes.

Q. And you're not?

A. That is right.

Ex. 4, 98:15-99:16. These opinions regarding clinical diagnoses and outcomes are particularly improper, given that Dr. Thisted has no medical degree and has never treated a patient.

As discussed above, the Federal Circuit has made clear that a non-POSA expert should not be permitted to testify regarding issues that are analyzed from a POSA's perspective, such as patent validity. *E.g.*, *Kyocera*, 22 F.4th at 1376-78. Accordingly, Dr. Thisted's opinions regarding the validity of Asserted Claims, including at least those identified in Exhibit 1, should be excluded.

**C. Dr. Thisted's Opinions regarding Infringement Should be Excluded**

Dr. Thisted did not submit an opening report regarding infringement, an issue on which UTC bears the burden of proof, and instead addressed infringement for the first time on reply in his 197-page Reply Report. *See generally* Ex. 2; D.I. 45, ¶ 9.a (setting opening report deadline for issues on which the party "has the initial burden of proof on the subject matter"). Dr. Thisted does not rely on, nor does he adopt, any of the opinions in Dr. Nathan's Opening Report regarding infringement. Ex. 4, 16:1-15, 28:10-14. Instead, he undertakes an independent—and highly duplicative—assessment of infringement from the perspective of a POSA.<sup>5</sup> This is improper under Rule 702 and Federal Circuit case law, as Dr. Thisted is not a POSA. *Kyocera*, 22 F.4th at 1376-78; *Sierra Wireless*, 130 F.4th at 1024-25.

Dr. Thisted acknowledges in his Reply Report that "patent infringement is evaluated from the perspective of a hypothetical person of ordinary skill in the art ('POSA')" and admitted during deposition that he is not a POSA in this case. Ex. 2, ¶ 19; Ex. 4, 23:9-25:10. And yet, Dr. Thisted's Reply Report opines at length regarding whether a POSA would consider Liquidia's Yutrepia<sup>TM</sup> product to infringe the Asserted Claims of the '327 patent. *See generally* Ex. 2; *e.g.*, *id.*, at ¶¶ 223, 228-229, 235, 242, 250-251, 253-254, 275-277, 285-287, 309.

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<sup>5</sup> Liquidia intends to file a motion *in limine* to exclude portions of Dr. Thisted's Reply Report that are needlessly cumulative of Dr. Nathan's Opening and Reply Reports under Rule 403. *See Sanofi v. Glenmark Pharms. Inc.*, No. 14-264-RFA, 2016 WL 10957311, at \*2 (D. Del. May 12, 2016) ("[I]t is this Court's practice not to allow duplicative testimony from experts. I expect that Plaintiffs will utilize Dr. Thisted's testimony as appropriate, and not merely to repeat or buttress Dr. Reiffel's testimony.").

For example, Dr. Thisted asserts that “a POSA would recognize that the results of the INCREASE trial provide a reliable guide as to clinical outcomes of inhaled treprostinil, whether Tyvaso or Yutrepia.” *Id.* at ¶ 223. He also repeatedly opines that “a POSA’s reading” of the Yutrepia<sup>TM</sup> label and/or the INCREASE study would not be “so limited” in the manner articulated by Liquidia’s POSA expert, Dr. Richard Channick. *Id.* at ¶¶ 254, 261, 270, 276, 287, 295, 310, 317, 318; *see also id.* at ¶¶ 251, 267, 283, 292, 306 (asserting that “there is no scientific basis for Dr. Channick’s attempts to disassociate Yutrepia<sup>TM</sup> from the INCREASE study’s outcomes”). Additionally, he speculates as to how a POSA would interpret the Asserted Claims, a necessary step for determining infringement, including what steps the Asserted Claims require. *Id.* at ¶¶ 228, 235 (opining that the Asserted Claims do not require a healthcare provider or patient to “actively measure” whether Yutrepia<sup>TM</sup> administration produces the claimed statistically significant outcomes); *see also, e.g., id.* at ¶¶ 228-229, 237, 252, 285, 293, 308. Based on these and other speculative assessments of a POSA’s beliefs and actions, Dr. Thisted reaches his ultimate conclusions that Liquidia’s Yutrepia<sup>TM</sup> product “will infringe” the Asserted Claims. *See generally* Ex. 2, § VII.A-N; *see also, e.g., id.* at ¶ 309 (opining that “it is more likely than not that PH-ILD patients, especially those within the IIP and IPF subpopulations, . . . will experience an inhaled treprostinil treatment effect . . .”). Dr. Thisted also impermissibly opines about knowledge he believes a POSA would have, and actions he believes a POSA would take, based on the content of the Yutrepia<sup>TM</sup> label, as part of rendering his opinions on induced infringement. *E.g., id.* at ¶¶ 237, 239-240, 243, 245, 266, 282, 285, 293, 305; *see also generally id.* at § VII.A-N.

Dr. Thisted has no scientific or personal basis to make these assertions regarding the POSA’s perspective, rendering his infringement opinions inadmissible under Rule 702. *See Kyocera*, 22 F.4th at 1376-77 (finding that the opinions of a non-POSA expert are “neither relevant

nor reliable” and “not [] based on any specialized knowledge, training, or experience that would be helpful to the fact-finder”); *see also Bausch*, 2025 WL 591318, at \*2-6 (applying Rule 702 to exclude testimony regarding infringement from non-POSA expert); *see, e.g., Ex. 2*.

The circumstances here are distinguishable from those in *Sanofi v. Glenmark Pharms. Inc.*, No. 14-264-RFA, 2016 WL 10957311 (D. Del. May 12, 2016), where this Court permitted Dr. Thisted to testify regarding “how medical professionals interpret clinical trial data.” *Id.* at \*1. There, the Court found that “Dr. Thisted has technical expertise on a relevant aspect of the pertinent art,” even though he did not meet the POSA definition. *Id.* Here, in contrast, Dr. Thisted opines on subject matter beyond his technical expertise, including infringement, validity, clinical diagnosis of PH-ILD patients, and treatment of PH-ILD. *See supra* § III.C. Further, since the 2016 *Sanofi v. Glenmark* decision, the Federal Circuit in 2022 clarified that an expert witness “must at least have ordinary skill in the art” to offer expert testimony regarding patent validity. *Kyocera*, 22 F.4th at 1376-78. Lastly, the Defendants in *Sanofi v. Glenmark* sought to exclude the entirety of Dr. Thisted’s opinions; here, Liquidia only seeks to exclude specifically identified opinions of Dr. Thisted where he exceeds his domain of expertise and opines from the perspective of a POSA. *See Sanofi v. Glenmark Pharms. Inc.*, No. 14-264-RFA, D.I. 250 at 6 (D. Del.) (stating that Dr. Thisted’s “opinions should be entirely excluded”); *cf. Ex. 1 and Ex. 2*.

Moreover, Dr. Thisted’s objectionable opinions do not rely on the opinions of UTC’s POSA experts in this case, Drs. Nathan and Wertheim, who are both medical doctors with experience treating patients. *See supra* § III.B. Instead, as examination of Dr. Thisted’s Rebuttal and Reply Reports reveals, Dr. Thisted offers his opinions without any reliance on the opinions of UTC’s clinician experts, but instead offers his views independently. Further, Dr. Thisted admits that he did not speak with either Dr. Nathan or Dr. Wertheim in preparing his reports. *Ex. 4, 16:1-15*,

28:10-14. Thus, any belated attempt by UTC to piggyback Dr. Thisted's opinions onto those of its medical doctor experts cannot save Dr. Thisted's opinions from exclusion.

In sum, Dr. Thisted's opinions regarding validity and infringement should be excluded because he does not qualify as a POSA. *Kyocera*, 22 F.4th at 1376-78.

**D. Alternatively, Dr. Thisted's Identified Opinions Should be Excluded under Rules 402 and/or 403**

In the event the Court views the issues presented herein as more appropriate for a motion *in limine*, Liquidia respectfully requests that the Court exclude Dr. Thisted's identified opinions under Rules 402 and/or 403. As explained above, Dr. Thisted purports to provide expert testimony regarding whether a POSA would consider the Asserted Claims valid and infringed—but he admittedly is not a POSA. *See supra* §§ III, IV.B-C. His opinions are therefore irrelevant to the issues of validity and infringement, and thus inadmissible under Rule 402. *Kyocera*, 22 F.4th at 1377 (holding that a non-POSA expert's opinions regarding validity and infringement are “neither relevant nor reliable”); *see also* Fed. R. Evid. 402.

Additionally, under Rule 403, Dr. Thisted's non-POSA opinions regarding a POSA's perspective are unfairly prejudicial to Liquidia, and risk confusing the issues. *See Kyocera*, 22 F.4th at 1376-77 (holding that admitting expert testimony regarding infringement or validity from a non-POSA “serves only to cause mischief and confuse the factfinder”) (quoting *Sundance*, 550 F.3d at 1362); *see also* Fed. R. Evid. 403. Allowing an expert lacking ordinary skill in the art to testify regarding a POSA's beliefs “would ‘amount[] to nothing more than advocacy from the witness stand.’” *Id.* (quoting *Sundance*, 550 F.3d at 1364-65). Dr. Thisted's identified opinions would further waste time because they serve “merely to repeat or buttress” the testimony of Dr. Nathan, UTC's POSA expert. *See Sanofi*, 2016 WL 10957311, at \*2; *see also Robert S. v. Stetson Sch.*, 256 F.3d 159, 169-71 (3d Cir. 2001) (affirming district court's limit on expert testimony

regarding the same issues already addressed by another expert). Accordingly, any potential relevance of Dr. Thisted's testimony regarding a POSA's perspective is substantially outweighed by the risk of unfairly prejudicing Liquidia, confusing the issues, and wasting time, and should be excluded under Rule 403.

## V. CONCLUSION

For the reasons explained above, the Court should grant Liquidia's motion to exclude Dr. Thisted's opinions regarding infringement and validity under Rule 702 or, alternatively, under Rules 402 and/or 403.

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**CERTIFICATE OF SERVICE**

I hereby certify that on April 4, 2025, this document was served on DG-ILD@goodwinlaw.com, UTCvLiquidia-Del-23cv975@mwe.com and the persons listed below in the manner indicated:

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# EXHIBIT 1



**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

UNITED THERAPEUTICS  
CORPORATION,

Plaintiff

V.

LIQUIDIA TECHNOLOGIES, INC.,

Defendant.

C.A. No. 1:23-cv-00975-RGA

**HIGHLY CONFIDENTIAL**

## REBUTTAL EXPERT REPORT OF RONALD A. THISTED, PH.D.

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## TABLE OF ABBREVIATIONS

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'327 patent	U.S. Patent No. 11,826,327 (UTC PH-ILD 005310)
'793 patent	U.S. Patent No. 10,716,793 (UTC PH-ILD 009772)
'810 Provisional App.	U.S. Provisional Patent Application No. 63/011,810 (UTC PH-ILD 069472)
'611 Provisional App.	U.S. Provisional Patent Application No. 63/160,611
Expert Reports	
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Hill Op. Rept.	2024-12-20 Expert Report of Dr. Nicholas Hill
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Echt 1991	Debra S. Echt et al., <i>Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo</i> , 324 N. Eng. J. Med. 781 (1991)
Faria-Urbina 2018	Mariana Faria-Urbina et al., <i>Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease</i> , 196(2) Lung 139 (2018) (UTC PH-ILD 009936)
Faria-Urbina 2018 Supplementary Material	Supplementary Material for Mariana Faria-Urbina et al., <i>Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease</i> , 196(2) Lung 139 (2018)
Feb. 2020 Press Release	Press Release, United Therapeutics Announces <i>INCREASE</i> Study of Tyvaso® Meets Primary and All Secondary Endpoints (Feb. 24, 2020) (UTC LIQ00063612)
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Kallmes 2009	Kallmes DF et al., <i>A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures</i> , 361 N. Eng. J. Med. 569 (2009)
Lettieri 2006	Christopher J. Lettieri et al., <i>Prevalence and Outcomes of Pulmonary Arterial Hypertension in Advanced Idiopathic Pulmonary Fibrosis</i> , 129 Chest 746 (2006) (UTC_PH-ILD_020775)
March 2015 Presentation	Mar. 9, 2015 Tyvaso in WHO Group 3 Proof of Concept Review (UTC_PH-ILD_082484)
Morganroth 1990	Joel Morganroth et al., <i>Treatment of Ventricular Arrhythmias by United States Cardiologists: A Survey Before the Cardiac Arrhythmia Suppression Trial Results Were Available</i> , 65 Am. J. Cardiology 40 (1990)
Morton & Torgerson 2003	Veronica Morton & David J Torgerson, <i>Effect of Regression to the Mean on Decision Making in Health Care</i> , 326 BMJ 1083 (2003)
Naggie 2022	Susanna Naggie et al., <i>Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19</i> , 328 JAMA 1595 (2022)
Nathan 2024	Steven D. Nathan et al., <i>Inhaled Treprostinil in Pulmonary Hypertension Associated With COPD: PERFECT Study Results</i> , 63 Eur. Respiratory J. (2024)
NCT02630316 Version 1	Version 1 of ClinicalTrials.gov Posting for “Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE” (NCT02630316) (Dec. 15, 2015)
NCT02630316 Version 24	Version 24 of ClinicalTrials.gov Posting for “Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE” (NCT02630316) (Mar. 3, 2017)
NCT02630316 Version 85	Version 85 of ClinicalTrials.gov Posting for “Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE” (NCT02630316) (Jan. 10, 2020)
NCT02630316 Version 88	Version 88 of ClinicalTrials.gov Posting for “Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE” (NCT02630316) (June 2, 2020)
NCT02630316 Version 89	Version 89 of ClinicalTrials.gov Posting for “Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE” (NCT02630316) (May 24, 2021)
NCT03496623 Version 1	Version 1 of ClinicalTrials.gov Posting for “A Phase 3 Adaptive Study to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Participants With Pulmonary Hypertension (PH) Due to Chronic Obstructive Pulmonary Disease (COPD) (PERFECT)” (NCT03496623) (Apr. 12, 2018)
Parikh 2016	Kishan S. Parikh et al., <i>Safety and Tolerability of High-dose Inhaled Treprostinil in Pulmonary Hypertension</i> , 67 J.

	Cardiovascular Pharmacology 322 (2016) (unpublished manuscript) (UTC PH-ILD 010599)
Sackett 1989	D. L. Sackett, <i>Rules of Evidence and Clinical Recommendations on the Use of Antithrombotic Agents</i> , 95 Chest 2S (1989)
Sackett 1995	David L. Sackett & William M. C. Rosenberg, <i>On The Need for Evidence-Based Medicine</i> , 4 Health Econ. 249 (1995)
Saggar 2014	Rajeev Saggar et al., <i>Changes in Right Heart Haemodynamics and Echocardiographic Function in an Advanced Phenotype of Pulmonary Hypertension and Right Heart Dysfunction Associated With Pulmonary Fibrosis</i> , 69 Thorax 123 (2014) (LIQ PH-ILD 00000226)
Torres-Saavedra & Winter 2022	Pedro A. Torres-Saavedra & Kathryn A. Winter, <i>An Overview of Phase 2 Clinical Trial Designs</i> , 112 Int'l J. Radiation Oncology, Biol., Physics 22 (2022)
Wallace 2022	Sowdhamini S. Wallace et al., <i>Hierarchy of Evidence Within the Medical Literature</i> , 12 Hospital Pediatrics 745 (2022)
Waxman 2021	Aaron Waxman et al., <i>Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease</i> , 384 N. Eng. J. Med. 325 (2021) (UTC PH-ILD 010790)
Xu 2022	Jiuyang Xu & Bin Cao, <i>Lessons Learnt from Hydroxychloroquine/Azithromycin in Treatment of COVID-19</i> , 59 Eur. Respiratory J. 2102002 (2022)
2017 INCREASE Study Description	Version 23 of ClinicalTrials.gov Posting for “Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE” (NCT02630316) (Feb. 10, 2017) (LIQ PH-ILD 00000185)
2017 Waxman Tr.	Transcript of 12th Annual John Vane Memorial Symposium, March 17, 2017 (LIQ PH-ILD 00147328)
2018 Waxman Tr.	Thomson Reuters Streetevents Edited Transcript UTHR – United Therapeutics Corp to Host Science Day 2018, September 24, 2018 (LIQ PH-ILD 00140569)

## I. INTRODUCTION

1. I, Ronald A. Thisted, Ph.D., have been asked by Plaintiff United Therapeutics Corporation (“UTC”) to provide my expert opinion in the above-captioned litigation concerning the validity of certain claims of U.S. Patent No. 11,826,327 (“the ’327 patent”). I understand that in the above-captioned litigation, UTC asserts that Defendant Liquidia Technologies, Inc. (“Liquidia”) infringes claims 1-11 and 14-19 of the ’327 patent (the “Asserted Claims”). I understand that, in response, Liquidia asserts that each of the Asserted Claims is invalid and unenforceable.

2. UTC has asked me to analyze certain opinions expressed in the Expert Report of Dr. Richard Channick (the “Channick Report”) and the Expert Report of Dr. Nicholas Hill (“the Hill Report”), both of which were submitted on behalf of Liquidia on December 20, 2024. More specifically, UTC has requested that I review and respond to opinions offered by Drs. Hill and Channick that the Asserted Claims are invalid. I submit this Rebuttal Expert Report (“Rebuttal Report”) to provide my expert opinions regarding the validity of the Asserted Claims of the ’327 patent and the bases for the opinions.

3. As explained below, I disagree with the opinions of both Dr. Channick and Dr. Hill that the Asserted Claims are invalid as either anticipated or obvious.

4. I understand that I may be expected to testify on these opinions, as set forth in this Rebuttal Report, and in any Supplemental Expert Reports that I may prepare for this case in the future. I also understand that I may be expected to testify with respect to arguments raised by Liquidia in its Opening Report or matters addressed by any expert testifying on behalf of Liquidia in response to this Rebuttal Report.

5. I reserve the right to supplement or modify the opinions expressed in this Rebuttal Report, as well as the basis for my opinions, depending on the nature and content of the proofs

presented by Liquidia and any other information subsequently provided by Liquidia, Liquidia's expert(s), and/or discovered by UTC. I further reserve the right to use animations, demonstratives, enlargements of actual exhibits, and other information in order to illustrate my opinions.

## **II. QUALIFICATIONS**

6. I have more than fifty years of research, academic, and practical experience in the area of biostatistics. My research has focused on biostatistics and epidemiology, study design, statistical computation, and the effectiveness of medical interventions.

7. I am Professor Emeritus in the Department of Statistics and the Department of Public Health Sciences at the University of Chicago. At the time of my retirement in 2018, I also held faculty appointments in the Department of Anesthesia & Critical Care and the Committee on Clinical Pharmacology and Pharmacogenomics.

8. I received a bachelor's degree (B.A.) in mathematics and philosophy in 1972 from Pomona College in Claremont, California. In 1973 and 1977, respectively, I received a master's degree (M.S.) and a Doctor of Philosophy degree (Ph.D.) in statistics at Stanford University in Palo Alto, California.

9. I have held positions on the faculty of the University of Chicago since 1976. I was Co-Director of the Clinical Research Training Program (1999–2012), Chairman of the Department of Health Studies [now Public Health Sciences] (1999–2012), Director of Population Sciences for the Institute for Translational Medicine (2007–2014), and Scientific Director for the Biostatistics Core Facility at the University of Chicago Cancer Research Center (1999–2014).

10. From 2014 until my retirement, I was Vice Provost for Academic Affairs at the University of Chicago.

11. I have taught courses on statistics and biostatistics for over fifty years. I have also taught courses on statistical methods, computation, epidemiology, and clinical research methods.

I have been awarded the Llewellyn John and Harriet Manchester Quantrell Award for Excellence in Undergraduate Teaching. For thirteen years I co-taught a year-long course in clinical research methods to advanced medical trainees and to junior faculty in the Pritzker School of Medicine.

12. Among the courses that I have taught, for fifteen years I taught a course that was required for all first-year medical students in the Pritzker School of Medicine at the University of Chicago. This course, initially titled “Medical Statistics” and then “Epidemiology and Clinical Investigation” focused on assessment of clinical evidence, critical appraisal of the medical literature, and the relative merits and drawbacks of the study designs most commonly used in the medical literature.

13. From 1983 through 1997 (excepting one year during which I was at Stanford University on sabbatical leave from the University of Chicago) I served as a member of the Institutional Review Board at the University of Chicago, which reviewed all proposed research in human subjects, including clinical research, at the University.

14. I am an Elected Fellow of the American Association for the Advancement of Science (1992) and of the American Statistical Association (1988). I have also been a member of several professional societies related to statistics and computation, including the Association for Computing Machinery, the International Biometric Society, the Institute of Mathematical Statistics, the Royal Statistical Society, and the Society for Industrial and Applied Mathematics.

15. I have authored over one hundred publications in the areas of statistics, biostatistics and epidemiology in peer-reviewed journals including the *New England Journal of Medicine*, the *Journal of the American Medical Association*, *The Lancet*, *Annals of Statistics*, *Journal of the American Statistical Association*, *Biometrika* and *Statistical Science*. I have written a book in the field of statistical computation, *Elements of Statistical Computing* (CRC Press, 1988). I have also

written over 35 book chapters, comments, reviews and other publications. I served as Associate Editor of the *Journal of the American Statistical Association* (1979–1985, 1987–1988) and of *ACM Transactions on Mathematical Software* (1990–1992).

16. I have served as Database Editor (1994), Managing Editor (1995), and Editor (1996–1998) for *Current Index to Statistics*. I sat on the editorial board of *SIAM Journal of Scientific and Statistical Computing* from 1983 to 1985. I have served as a referee for several journals on topics related to biostatistics, including *Annals of Applied Statistics*, *Regulatory Pharmacology and Toxicology*, *PLoS One*, and *Statistics in Medicine*. As a journal referee, I reviewed submitted articles for scientific quality. I have also acted as a referee for the National Institutes of Health (NIH) and the National Science Foundation (NSF). As a referee for NIH and NSF, I reviewed grant proposals for potential funding.

17. Since 1971 I have collaborated with physicians and other healthcare professionals in designing clinical studies, collecting data for those studies, and interpreting the results of their studies as well as published studies. Since 1976 many of these close collaborations have led to peer-reviewed publications in the clinical literature on which I am co-author.

18. Since the late 1970s, I have consulted for the pharmaceutical and medical device industries on the design of clinical trials, as well as the statistical analysis of results from clinical trials and other clinical and preclinical studies. This work has included consulting regarding the design and analysis of Phase I, Phase II, and Phase III clinical trials, designing and implementing data collection methods, supervising data coordinating centers, planning and overseeing statistical analysis of results, overseeing collection and analysis of adverse experience data, preparing reports for use by the U.S. Food and Drug Administration, and meeting with the FDA as part of the drug

development process. All of this work has been done in close collaboration with physicians, subject-matter experts, and other scientists.

19. My qualifications for forming the opinions set forth in this declaration are explained in more detail in my *curriculum vitae*, which is attached as Exhibit A. A list of cases during the previous 4 years in which I have testified as an expert at trial or by deposition is attached as Exhibit B.

### **III. COMPENSATION**

20. I am being compensated at my normal rate of \$950 per hour in connection with this case. My compensation is not contingent on the outcome of this case or on the substance of my opinions. I have no personal interest in the outcome of this case.

### **IV. MATERIALS RELIED UPON AND BASES FOR MY OPINIONS**

21. I have relied upon a number of materials in rendering the opinions in this declaration, including the Channick Report, the Hill Report, and materials cited therein. A complete list of such materials is provided in Exhibit C.

22. I have further relied on my knowledge, education and training and my many years of experience in the fields of biostatistics and epidemiology, as reflected in my qualifications and credentials set forth above and in my *curriculum vitae*.

23. To the extent I cite to only certain portions of a reference, I reserve the right to rely on the entirety of that reference. Where I cite a particular figure or chart, the citation should be understood to encompass any text referring or relating to that figure or chart, in addition to the figure or chart itself. Similarly, where a cited portion of text refers to a figure or chart, the citation should be understood to include the figure or chart as well. I also rely on my knowledge to provide context, and to aid in understanding and interpreting the portions of the evidence that are cited.

## V. ASSIGNMENT AND SUMMARY OF MY OPINIONS

24. I have been asked to review references identified and relied-up by Liquidia's experts, analyze them in view of biostatistics principles, and provide my opinion as to the validity of the Asserted Claims. As part of that analysis, I have been asked to analyze and respond to certain opinions offered by Dr. Channick and Dr. Hill regarding the clinical use of treprostinil prior to April 17, 2020, e.g., as described in the Saggar 2014<sup>1</sup>, Agarwal 2015<sup>2</sup>, Parikh 2016<sup>3</sup>, and Faria-Urbina 2018<sup>4</sup> references as well as the testimony of several clinicians that were deposed in connection with this case. Below, I will review the accounts of clinical treprostinil use cited by Dr. Channick and Dr. Hill and assess what (if any) any conclusions from them would have been warranted prior to the completion of the INCREASE trial. Included in this analysis will be an examination of the limitations presented by observational, unblinded, uncontrolled, single-center human studies as compared to randomized, blinded, placebo-controlled, multi-center phase III clinical trials such as the INCREASE Study. Finally, I will apply this analysis to respond to Dr. Channick's and Dr. Hill's positions on anticipation and obviousness. As I explain in more detail below, I disagree with both Dr. Channick and Dr. Hill that the Asserted Claims are invalid.

## VI. LEGAL PRINCIPLES

25. I am not an attorney, and I will offer no opinions on the law. I have, however, been instructed by counsel regarding the following legal principles related to my opinions. Based on

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<sup>1</sup> Rajeev Saggar et al., *Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis*, 69(2) Thorax 123 (2014) (LIQ\_PH-ILD\_00000226) ("Saggar 2014").

<sup>2</sup> Kishan S. Parikh et al., *Safety and Tolerability of High-dose Inhaled Treprostinil in Pulmonary Hypertension*, 67(4) J Cardiovasc Pharmacol (2016) (UTC\_PH-ILD\_010599) ("Parikh 2016").

<sup>3</sup> M. Agarwal & A.B. Waxman, (959) - *Inhaled Treprostinil in Group-3 Pulmonary Hypertension*, 34(4) J Heart Lung Transplant S343 (2015) (UTC\_PH-ILD\_009828) ("Agarwal 2015").

<sup>4</sup> Mariana Faria-Urbina et al., *Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease*, 196(2) Lung 139 (2018) (UTC\_PH-ILD\_009936) ("Faria-Urbina 2018").

these instructions, I have developed and applied the following understandings in arriving at my stated opinions and stated conclusions in this declaration.

**A. Validity of Patent Claims**

26. I understand that patents issued by the USPTO are presumed to be valid. I therefore understand that Liquidia, as the accused infringer, bears the burden of proving invalidity by “clear and convincing evidence.” I am informed that the clear and convincing evidence standard is met when the fact finder is left with a clear conviction that invalidity is highly probable.

27. I am informed that each claim of a patent is considered to be its own invention, and that as a result, validity is determined on a claim-by-claim basis.

28. I understand that determining the validity of a patent claim requires a two-step analysis. First, the claim language must be properly construed to determine its scope and meaning. Second, the claims, as properly construed, must be evaluated under the relevant legal standards, discussed below. I understand that, depending on the analysis to be performed, the claims may be compared to the “prior art” and/or the disclosures in the patent’s specification. In general, I understand from counsel that “prior art” references are public references that pre-date the patent and qualify as prior art under certain statutes. Examples include publications available prior to the filing of the patent application and certain patents.

**B. Person of Ordinary Skill in the Art (POSA)**

29. I understand that the validity of a patent is to be assessed from the perspective of a hypothetical person of ordinary skill in the art (“POSA”) as of the effective filing date. I understand that factors such as the education level of those working in the field, the sophistication of the technology, the types of problems encountered in the art, the prior art solutions to those problems, and the speed at which innovations are made inform the relevant level of skill in the art. I further understand that in addition to their own knowledge and skill, the POSA may work in

conjunction with other relevant individuals. Here, that group would have had experience in the related fields of, pharmacology, medical imaging, and biostatistics among others. The POSA would have had access to and/or consulted with, as needed, one or more members of a team of experienced professionals in these related fields.

30. As discussed below, the Asserted Claims of the '327 patent generally relate to methods of “improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease” by administering treprostinil via oral inhalation.<sup>5</sup>

31. For the purposes of this Rebuttal Report, I have been instructed by counsel to assume that the effective filing date of the '327 patent is April 17, 2020, which corresponds to the filing date of the earliest provisional application to which the '327 patent claims priority.<sup>6,7</sup>

32. I understand that, as part of claim construction in this matter, discussed below, UTC and Liquidia each proposed a definition of the POSA for purposes of the '327 patent. The parties' respective positions from their Joint Claim Construction Brief are reproduced below:<sup>8</sup>

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<sup>5</sup> *Infra* § VIII.

<sup>6</sup> *Infra* § VIII.

<sup>7</sup> UTC has not asked me to assess the effective filing date of the '327 patent, and I have not formed any opinions in this regard. I understand that Liquidia and Dr. Channick have taken the position that the earliest effective filing date to which the '327 patent is entitled is March 12, 2021, which corresponds to the filing date of the second provisional application to which the '327 patent claims priority. *See, e.g.*, Channick Op. Rept. ¶ 95. My opinions as set forth below—which primarily concern the conclusions a medical professional could draw from observational studies of treprostinil prior to INCREASE—would not change if the Court were to adopt Liquidia's proposed effective filing date.

<sup>8</sup> Redacted Version of D.I. 123, Joint Claim Construction Brief (“D.I. 127”) at 4.

**A. Plaintiff's Opening Position**

The '327 patent is directed to methods of improving exercise capacity in a patient having PH-ILD. The POSA would have a graduate degree in medicine or a field relating to drug development, such as an M.D. or a Ph.D., with at least two years' experience treating patients with interstitial lung disease, including with PH-ILD. D.I. 26 at 6.

**B. Defendant's Answering Position**

A person of ordinary skill in the art ("POSA") would have a medical degree with a specialty in pulmonology or cardiology, plus at least two years of experience treating patients with PH as an attending, including PH-ILD and including with inhaled therapies, or equivalent degree or experience. *See* D.I. 54, ¶ 24.

33. I have both formal and practical education in statistics and biostatistics, and have taught and consulted in those areas for decades. For more than 50 years I have been involved in analyzing data collected from human clinical studies as well as designing clinical trials themselves. My experience spans a variety of different functional areas, including cardiovascular health. Throughout my career, it has been my regular practice to work closely with practicing physicians and advise them as to both the interpretation of clinical study results and the design of the clinical investigations, including clinical trials, themselves.<sup>9</sup> For example, I have frequently worked with physicians to select and design the key parameters associated with a clinical trial (e.g., placebo controls, length of treatment, endpoints, exclusion criteria, inclusion criteria, etc.) and then subsequently consult with the physicians running the trial while it is in progress. After a trial is complete, I typically perform a biostatistical analysis of the resulting data, which includes, for

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<sup>9</sup> I understand that one of the inventors of the '327 patent, Dr. Chunqin ("C.Q.") Deng, is a biostatistician and fulfilled a similar role in the design and analysis of the INCREASE trial described in the '327 patent. *See* Excerpt of 2024-11-12 Chunqin Deng Deposition Transcript ("Deng Dep. Tr.") at 53:9-19; 2024-03-04 D.I. 035 Redacted Version of 2024-02-26 D.I. 28 Declaration of Steven D. Nathan, M.D ("Nathan PI Decl.") at ¶ 27.

example, determining whether the data for particular endpoints are statistically significant. Throughout my career, I have worked alongside and advised physicians who met the level of skill of the POSA under either party's definition for various diseases, *i.e.*, those with the education and experience levels described in the parties' definitions, including experience with cardiologists and pulmonologists on a range of conditions or experience at that level of skill but with other diseases. As noted above, I also spent years teaching future MDs about biostatistics and assessment of clinical data. I am therefore familiar with the perspective of a POSA in this case, particularly as it relates to how a POSA would analyze and understand clinical data. Based on my qualifications outlined above,<sup>10</sup> and in this section, I am able to provide opinions reflecting the perspective of a hypothetical POSA under either party's definition. The opinions offered in this report reflect those of the POSA. My opinions as set forth below would not change regardless of which above POSA definition the Court adopts.

### **C. Anticipation**

34. I understand from counsel that a patent claim is invalid as "anticipated" if none of the elements of that claim, either individually or in combination with each other, is new or novel. I understand that a claim may be anticipated in at least three different ways: (1) disclosure in the prior art; (2) prior sale; and (3) prior public use.

#### **1. Anticipation By Prior Art Disclosure**

35. I understand from counsel that a patent claim is anticipated by *prior disclosure* if all of the elements of that claim were disclosed in a single disclosure in the prior art (e.g., in a printed publication or a patent). I also understand that anticipation in this context requires an

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<sup>10</sup> *Supra* § II.

“enabling disclosure” such that a POSA could practice every element of the claimed invention without undue experimentation.

36. I understand that anticipation may be by express disclosure in the prior art. I also understand that if the prior art reference does not expressly set forth a particular claim element, the reference may still anticipate a patent claim if that element is “inherent” in its disclosure. With respect to method claims, I understand that a result is inherent if it is a necessary and inevitable consequence of practicing the claimed method.

37. I understand that only a single reference should be relied upon to conclude that a claim is anticipated, unless any further references are cited solely to: (a) prove that the primary reference contains an “enabling disclosure”; (b) explain the meaning of a term used in the primary reference; or (c) show that a characteristic not disclosed in the reference is inherent. I understand that to anticipate a claim, the prior art does not need to use the same words as the claim, but all of the requirements of the claim must have been disclosed, either stated expressly or implied to a person having ordinary skill in the art in the technology of the invention. I also understand that a narrower claim is not necessarily anticipated by a broader prior art reference if the claims contain additional elements not described by the broader reference.

## **2. Anticipation By Prior Public Use**

38. I understand from counsel that a patent claim is anticipated by *prior public use* if every element of the claimed invention was used in public prior to the effective filing date.

39. I understand that the use of an invention is considered “public” when that use is accessible to the public or where the inventor commercially exploits the use. I understand that a use of a claimed invention is accessible to the public if the claimed invention (or an obvious variant thereof) is shown to or used by an individual, other than an inventor, without limitation, restriction, or obligation of confidentiality. I understand that determining public accessibility considers the

nature of the use, whether there was public access to that use, and any observers' confidentiality obligations.

40. I understand that, for purposes of anticipation, an invention is not considered to have been used publicly if the invention is not "ready for patenting" at the time it was used. I am informed that an invention is ready for patenting when it is reduced to practice or when the inventor has prepared descriptions of the invention that are sufficiently specific to permit the POSA to practice the invention. I understand that reduction to practice of a method claim is only met when the inventor performs a process that meets all the limitations of the claim and the inventor has determined that the claimed method will work for its intended purpose. I understand that a claimed method's intended purpose does not need to be recited in the claim. I understand that the extent of testing necessary to verify that an invention works for its intended purpose depends on the claim language and the invention's character, which includes the nature and complexity of the problem the invention seeks to solve. I understand that an invention is not ready for patenting when there is a probability of failure.

41. I understand that prior public use of a claimed invention does not invalidate an issued claim if the use was experimental. I understand that experimental use includes testing or experimentation performed to perfect the claimed invention. I understand that the primary or substantial purpose of testing claimed features (or any features inherent to claimed features) must be for the purpose of determining whether the claimed invention works for its intended purpose. I understand that determining whether a use was an experimental use considers the totality of surrounding circumstances. I further understand that the following are relevant to assessing whether a use was experimental: the necessity for public testing; the amount of control over the experiment retained by the inventor; the nature of the invention; the length of the test period;

whether payment was made; whether there was a secrecy obligation; whether records of the experiment were kept; who conducted the experiment; the degree of commercial exploitation during testing; whether the invention reasonably requires evaluation under actual conditions of use; whether testing was systematically performed; whether the inventor continually monitored the invention during testing; and the nature of contacts made with potential customers.

### 3. Anticipation By Prior Sale

42. I understand from counsel that a patent claim is anticipated by *prior sale* if every element of the claimed invention was on sale prior to the effective filing date.

43. I understand that a claimed invention is considered to be “on sale” when the invention is (a) the subject of a bona fide commercial offer for sale, public or secret; and (b) and it is ready for patenting. I further understand that the “ready for patenting” standard is the same in the context of prior sale as it is in the context of prior public use (discussed above).<sup>11</sup>

44. I understand that the mere existence of a commercial benefit to an inventor does not equate to a commercial sale—the claimed invention itself must be sold or offered for sale. I understand that merely exchanging technical know-how or providing technical assistance regarding an inventive process does not put that inventive process on sale. I also understand that potential plans to commercialize an invention does not put that invention on sale.

45. I further understand that an inventive method may be on sale when the inventive method is commercially exploited, e.g., an inventive process is used to make the subject of a commercial sale or the inventive process is performed or offered to be performed for compensation. However, I understand that the essential features of the claimed inventive process must be substantially embodied in what is sold. I understand that products that have uses apart

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<sup>11</sup> *Supra* § VI. C. 2.

from use in an inventive process do not substantially embody the essential features of the inventive process. I further understand that agreements to perform a service are insufficient to demonstrate a claimed process was on sale unless those agreements require performance of the claimed method.

46. I understand a prior sale of the claimed invention will not invalidate an issued claim if that sale was for the purpose of experimental use. The same considerations for demonstrating prior public use apply to prior public sale.

**D. Obviousness**

47. I understand from counsel that a patent claim is invalid if the differences between the patented subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made. I also understand that the question of obviousness requires consideration of (a) the scope and content of the prior art; (b) the level of ordinary skill in the art; (c) the differences between the claimed invention and the prior art; and (d) secondary considerations of non-obviousness. I further understand that the scope and content of the prior art must be viewed through the perspective of a POSA at the time of the invention.

48. Unlike anticipation, I understand that an obviousness analysis can be based on more than a single prior art reference. I understand, however, that when multiple references are used in combination to argue that a patent claim is obvious, every element (or limitation) of the claim must be disclosed, expressly or inherently, in that combination of references.

49. I understand that an obviousness analysis must be performed from the perspective of a POSA as of the effective filing date. I understand that a POSA is a person of ordinary creativity, not an automaton or a person with exceptional or extraordinary knowledge.

50. I have been instructed by counsel and understand that demonstrating obviousness requires more than merely showing that the prior art includes separate references covering each separate limitation in a claim under examination. I understand that a conclusion of obviousness

requires the additional showing that a person of ordinary skill at the time of the invention would have been motivated to select and combine those references, and, in making that combination, a person of ordinary skill in the art would have a reasonable expectation of success. I understand from counsel that obviousness of patent claims is examined at the time of the effective filing date based on the prior art without the benefit of the patent application. That is, the specification of the '327 patent is not available as prior art.

51. I understand that analyses that rely on hindsight to establish obviousness are improper. Counsel has therefore instructed me that when considering obviousness, I should not consider what is known today or what was learned from the asserted patent. Instead, I should put myself in the position of a POSA at the time of the claimed invention. In particular, I understand that it is improper to use the invention as a roadmap to find its prior art components, because that approach discounts the value of combining various existing features or principles in a new way so as to achieve a new result.

52. Finally, I understand that in forming an opinion regarding obviousness, one must consider so-called “objective indicia” of non-obviousness, which include, for example:

- a. Whether the invention was commercially successful as a result of the merits of the claimed invention (rather than the result of design needs or market-pressure advertising or similar activities;
- b. Whether the invention satisfied a long-felt need;
- c. Whether others had tried and failed to make the invention;
- d. Whether others invented the invention at roughly the same time;
- e. Whether others copied the invention;

- f. Whether there were changes or related technologies or market needs contemporaneous with the invention;
- g. Whether the invention achieved unexpected results;
- h. Whether others in the field praised the invention;
- i. Whether persons having ordinary skill in the art of the invention expressed surprise or disbelief regarding the invention;
- j. Whether others sought or obtained rights to the patent from the patent holder; and
- k. Whether the inventor proceeded contrary to accepted wisdom in the field.

The timeframe for evaluating these factors is not limited to the time of the invention, and post-invention evidence may be considered.

53. I understand that to be relevant to an obviousness inquiry, evidence of objective indicia must be attributable to, or a direct result of, the claimed invention. I am informed that this is referred to as the “nexus” requirement.

## **VII. SCIENTIFIC BACKGROUND**

54. My opinions below rely on basic concepts of statistics such as statistical significance, and on fundamental aspects of clinical study design such as the distinction between prospective and retrospective clinical studies, randomized clinical trials, and the importance of controls to eliminate bias. To assist the court, I provide an overview of these concepts in this section. I apply the principles discussed here in forming my opinions concerning the documents I was asked to review. If asked to testify, I may provide a tutorial on the background facts and scientific opinions that support my opinions. These and other background state-of-the-art concepts are described in detail below. I reserve the right to provide additional background information or detail as appropriate.

55. *Hierarchy of medical evidence.* Evidence-based medicine involves the practice of critical appraisal of publications in the medical literature to assess the quality of evidence about a given clinical question that each publication provides. Quality of evidence depends critically on the study design, and some designs are inherently of higher quality and more reliable than others. In 1969, David Sackett (often called the father of evidence-based medicine) outlined the levels of evidence associated with general classes of study design, from highest to lowest<sup>12</sup>:

<b>Table 1—The Relation Between Levels of Evidence and Grades of Recommendations</b>	
<b>Level of Evidence</b>	<b>Grade of Recommendation</b>
<b>Level I: Large randomized trials with clear-cut results (and low risk of error)</b>	<b>Grade A</b>
<b>Level II: Small randomized trials with uncertain results (and moderate to high risk of error)</b>	<b>Grade B</b>
<b>Level III: Nonrandomized, contemporaneous controls</b>	<b>Grade C</b>
<b>Level IV: Nonrandomized, historical controls</b>	
<b>Level V: No controls, case-series only</b>	

56. Of note, studies of medical treatments at all levels except for the lowest (Level V) entail comparisons against an appropriate control treatment. With respect to Level V studies (the category into which Saggat 2014,<sup>13</sup> Agarwal 2015,<sup>14</sup> Parikh 2016,<sup>15</sup> and Faria-Urbina 2018<sup>16</sup> all

<sup>12</sup> Sackett DL. *Rules of evidence and clinical recommendations on the use of antithrombotic agents*. Chest 1989; 95: 2S-4S. (“Sackett 1989”).

<sup>13</sup> Saggat 2014.

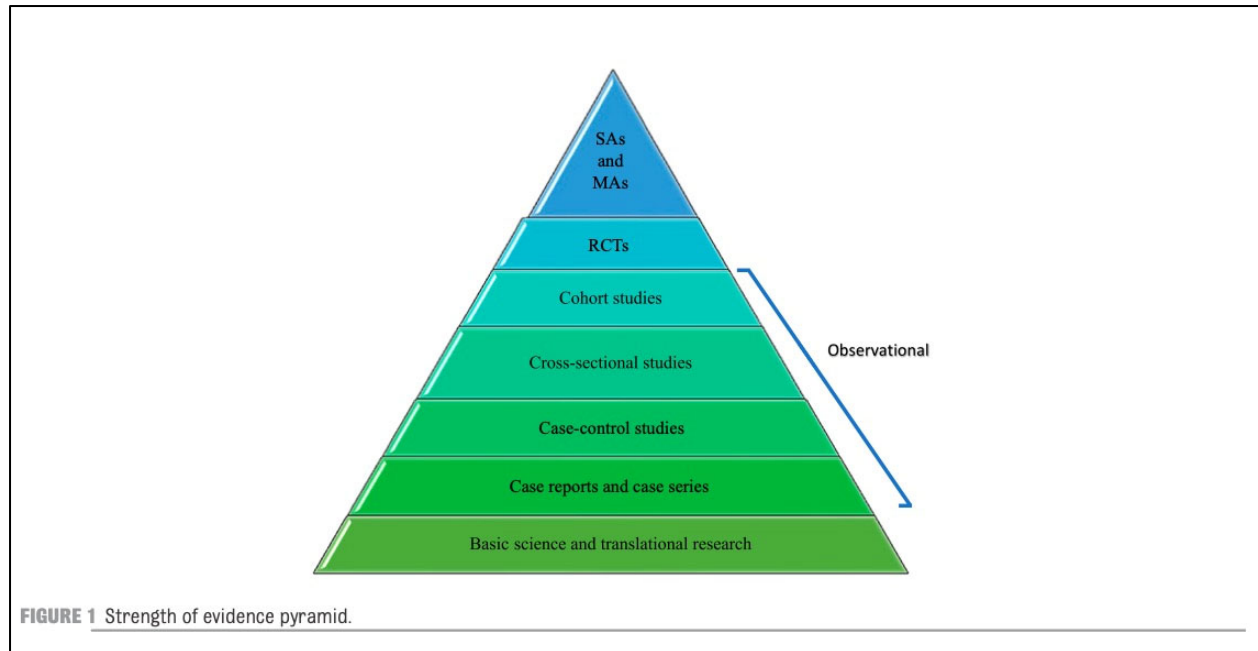
<sup>14</sup> Agarwal 2015.

<sup>15</sup> Parikh 2016.

<sup>16</sup> Faria-Urbina 2018.

fall), Sackett notes that for case series without controls, “the reader is simply informed about the fate of a group of patients. Such series may contain extremely useful information about clinical course and prognosis but can only hint at efficacy.”<sup>17</sup>

57. Sackett’s hierarchy has been refined to distinguish different kinds of studies within Level V.<sup>18</sup> A common extension is the “evidence pyramid” shown below.<sup>19</sup>



58. Here, too, except for non-human studies (which would fall into the category of “Basic science and translational research”), case series without controls provide the lowest level of evidence. Weber, *et al.*, note that “drawing conclusions from [case reports and case series] to answer clinical questions is not advised because of potential biases resulting from the small number of patients described and the lack of a comparison group.”<sup>20</sup>

<sup>17</sup> Sackett 1989 at 3S.

<sup>18</sup> Wallace SS, Barak G, Truong G, and Parker MW. *Hierarchy of Evidence Within the Medical Literature*, Hospital Pediatrics 2022. Aug 1;12(8):745-750. doi: 10.1542/hpeds.2022-006690 (“Wallace 2022”).

<sup>19</sup> Wallace 2022 at 748.

<sup>20</sup> Wallace 2022 at 746.

**A. Pulmonary Hypertension**

59. I reviewed a public, redacted version of a declaration of Dr. Nathan to learn about pulmonary hypertension, varieties thereof, and treatment options.<sup>21</sup>

**B. Study Design**

60. The kinds of questions that a study can answer, and the strength and validity of those answers, depends upon a number of factors which collectively are referred to as the “study design.” I will focus here on the design of clinical studies addressing the effectiveness of a medical treatment.

61. The conclusions that are warranted from a clinical study will depend upon key choices the principal investigators made in carrying out the clinical study. Important examples include:

- a) *Study population.* A clinical study’s inclusion and exclusion criteria identify the broader population of patients to whom the clinical study’s results may apply. For example, a clinical study conducted only in males cannot tell us about effectiveness in females. Similarly, a clinical study of a blood pressure treatment that includes patients either with or without diabetes cannot tell us about effectiveness in diabetics unless the clinical study explicitly reports results from diabetics separately from the broader population studied.
- b) *Treatment selection.* What treatment(s) will be studied, at what doses, and at what intervals?
- c) *Endpoints.* How will the results of treatment be measured (i.e., “outcome measures” or “endpoints”)? In particular, what tests, outcomes, or assessments will form the basis for any conclusion about effectiveness? How will the clinical study ensure that these assessments are carried out in the same way for all participants?

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<sup>21</sup> Nathan PI Decl.

- d) *Is the study descriptive or comparative?* Clinical studies that simply describe outcomes observed from patients who receive a particular treatment are called “descriptive” or “noncomparative.” Such clinical studies cannot determine whether some or all of the patient outcomes observed are the result of the treatment that patients received. That is because these clinical studies provide no information on how patients would have done had they not received the treatment. By way of contrast, clinical studies in which outcomes of patients receiving one treatment are compared to outcomes of patients receiving a control treatment (“comparative study”) provide a direct basis for assessing the potential relationship of outcomes to treatment. In such clinical studies, effectiveness is measured relative to a control treatment (*i.e.*, effectiveness is measured compared to placebo treatment or to another therapy). As described below, if there is only one treatment—and thus, no control treatment—effectiveness cannot be determined.
- e) *Treatment assignment method.* In clinical studies that compare two or more treatments, the way in which participants end up receiving one treatment or another is critical. For example, patients could be assigned at random to the various treatments, thereby ensuring that no factor that could affect the outcome of the clinical study systematically favors one treatment over another. By way of contrast, treatment assignment could be at the discretion of the treating physician, or patients could choose which treatment to receive, or patients who were already on one or the other of the treatments could be maintained on those treatments and observed during the clinical study. In cases such as the last three, bias that distorts the ultimate treatment comparison can easily arise. A common bias of this sort is called “confounding by indication,” in which the factors affecting choice of treatment are also factors that influence the outcome.

- f) *Time course of the clinical study.* Clinical studies in which investigators select patient participants, treat them (or observe treatment), and then follow patients forward in time to determine their outcomes are called “prospective” studies. Such clinical studies identify patients to include before the outcome has been experienced. It is possible to specify criteria to identify participants in a uniform manner, to prescribe specific procedures by which results will be obtained and evaluated, and to account for all patients entering the clinical study. By way of contrast, studies based on existing patient data originally collected for other reasons (medical records, for example) are described as “retrospective” studies. Retrospective studies are dependent on the assessments that are available in the records and are thus subject to several limitations. For example, investigators cannot determine whether assessments were carried out consistently, cannot adjust for (or even assess) sources of bias that arise from factors that were intentionally or unintentionally omitted from the data set (or that were unrecognized), or cannot control for extraneous variables that were not measured and thus are not present in the data set. Retrospective studies are also subject to a type of selection bias that arises because only some patients with the disease of interest are included in the clinical study.
- g) *Blinding.* In prospective clinical studies comparing two or more treatments, if the treatment each patient is on during the clinical study is concealed from the investigators, the clinical study is described as being “blinded” or “masked.”<sup>22</sup> Clinical studies in which investigators know the treatments for each patient are said to be “unblinded,” “unmasked,” or “open-label”

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<sup>22</sup> Blinded studies are often further described as single-, double-, or triple-blind. In a single-blind study, the identity of their treatment is not revealed to participants but is known to their treating physician. In a double-blind study, treatment assignment is concealed from both participants and investigators. In a triple-blind study, treatment assignment is concealed from participants, investigators, and data analysts. In the latter case, different treatments are distinguished for the data analysts using a code (e.g., treatments A and B) rather than the actual description of the treatments that those codes represent.

clinical studies. Blinding helps to ensure that a patient's treatment and evaluation during the course of the clinical study will not be influenced by anything the investigator may know about the treatment to which a patient is assigned. This is an important method for ensuring that differences between treatments are not resulting in part from differential treatment or evaluation of patients.

- h) *Sample size.* The number of participants included in a clinical study is referred to as the “study size” or “sample size.” Clinical studies with small sample sizes cannot reliably distinguish between actual treatment effects (“signal”) and the natural variation from patient to patient or occasion to occasion (“noise”). The reason that the randomized controlled trials that are required for showing the safety and effectiveness of drugs typically have large samples is that the noise induced by natural variability can be controlled and minimized.
- i) *Generalizability.* A clinical study may be carried out on the patients of a single investigator, or on patients seen at a single medical center, or on patients recruited at many geographically separated centers. The broader the patient population, the more generalizable results are likely to be and the less those results may be influenced by factors unique to a single investigator or a single institution.
- j) *Statistical methods.* A statistical analysis plan describes in advance of conducting the clinical study how the resulting data will be analyzed to answer the questions for which the clinical study was carried out. The choice of statistical analysis method can affect both the validity of the conclusions drawn and the precision with which effectiveness can be assessed. For instance, if patients drop out of a clinical study because their disease worsens and those patients are omitted from the clinical study's final analysis, then those results will be overly optimistic

because only patients doing relatively well end up being evaluated. Statistical methods that take account of dropouts can reduce or eliminate this source of bias.

62. In the following sections, I discuss specific elements of study design that affect the reliability of findings from the studies described in the articles I was asked to consider: Saggar 2014,<sup>23</sup> Agarwal 2015,<sup>24</sup> Parikh 2016,<sup>25</sup> and Faria-Urbina 2018.<sup>26</sup>

### **C. Single-arm case series**

63. The design of each of the four studies that I was asked to consider (those reported by Saggar 2014,<sup>27</sup> Agarwal 2015,<sup>28</sup> Parikh 2016,<sup>29</sup> and Faria-Urbina 2018<sup>30</sup>) is best described as a single-arm case series. Each reports only on patients receiving treprostinil and aspects of their clinical course are reported for some of those patients. Saggar 2014,<sup>31</sup> Agarwal 2015,<sup>32</sup> Parikh 2016,<sup>33</sup> and Faria-Urbina 2018<sup>34</sup> do not report any comparative studies. The reported study and chart reviews only involve subjects who were administered treprostinil, and thus these can be described as a “single-arm” “descriptive,” or “noncomparative” investigations.<sup>35</sup> Single-arm studies typically examine the average difference between baseline values of a measurement such as six-meter walking distance (“6MWD”) and the same measurement taken at a later point in time, with each measure taken in the same patient. The difference between the two measurements is

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<sup>23</sup> Saggar 2014.

<sup>24</sup> Agarwal 2015.

<sup>25</sup> Parikh 2016.

<sup>26</sup> Faria-Urbina 2018.

<sup>27</sup> Saggar 2014.

<sup>28</sup> Agarwal 2015.

<sup>29</sup> Parikh 2016.

<sup>30</sup> Faria-Urbina 2018.

<sup>31</sup> Saggar 2014.

<sup>32</sup> Agarwal 2015.

<sup>33</sup> Parikh 2016.

<sup>34</sup> Faria-Urbina 2018.

<sup>35</sup> *Supra* § VII. B.

known as a change score. Such noncomparative studies can suggest, but *cannot* establish, that any observed changes were the result of the treprostinil administration rather than due to other, non-treprostinil factors.

64. Indeed, noncomparative studies that rely on changes from baseline in a clinical performance measure, e.g., 6MWD, are particularly prone to bias and to potentially misleading results for at least two reasons.

65. First, the natural course of the disease (or aspects of clinical care other than the treatment under investigation) has the potential to cause changes in the outcome measure that are unrelated to the treatment being studied but which could wrongly appear to result from the treatment's effectiveness.

66. As an example, consider a noncomparative study of a method for treating symptoms of the common cold, and one of the study's endpoints is the change in severity of sneezing after ten days of treatment. The treatment method being studied is eating one green M&M daily for ten days. At the end of the ten-day period, sneezing would have disappeared in most or all of the patients studied, and thus it would appear that the treatment method—eating one green M&M daily for ten days—is effective. However, the change in the study's sneezing endpoint was actually attributable to another factor—the natural course of the disease—the common cold. Without some means of controlling for this non-M&M factor, the results would be misleading and therefore biased.

67. Of course, the natural course of disease is only one possible factor that could influence how symptoms change over time. Another factor, for instance, is the possibility that one or more other treatments are being used simultaneously that also contribute to symptom reduction.

If the patients in our hypothetical study were also taking common cold remedies, that too could account for the reduction in symptoms seen over ten days.

68. A real-life clinical example is the case of treating pain associated with compression fractures of the spinal vertebrae caused by osteoporosis. The treatment in question was to inject surgical-grade cement into the fractured bone on the unproven theory that doing so would provide support for the bone and cushioning of the nerve causing pain. This procedure, called vertebroplasty, was reported to be highly successful at alleviating pain in a series of articles comprising single-arm case series, as well as small unblinded nonrandomized cohort studies. This apparent success led to guidelines that recommended vertebroplasty for painful osteoporotic vertebral fractures. Only after a randomized, double-blind, placebo-controlled study was carried out did it become apparent that vertebroplasty caused no greater reduction in pain than a sham procedure in which nothing was done to the offending vertebra.<sup>36</sup> In the case of vertebroplasty, the authors of the clinical trial concluded<sup>37</sup> that

These results suggest that factors aside from the instillation of PMMA may have accounted for the observed clinical improvement after vertebroplasty. Such factors may include the effect of local anesthesia, as well as nonspecific effects, such as expectations of pain relief (the so-called placebo effect), the natural history of the fracture, and regression toward the mean.

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<sup>36</sup> Kallmes DF et al., *A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures*, 361 N. Eng. J. Med. 569 (2009) (“Kallmes 2009”).

<sup>37</sup> *Id.* at 575.

69. One means to control for these sources of bias would be to compare the results of M&M treatment to the results of patients *who were otherwise treated in the same manner*, but who were instructed to eat “placebo” M&Ms for ten days.

70. This principle of comparing efficacy results for a studied treatment to corresponding results from patients receiving a suitable control treatment is why FDA relies on “adequate and *well-controlled* studies” as the primary basis when it determines whether there is “substantial evidence” to support a claim that a drug is effective.<sup>38</sup> Moreover, FDA regulations state that “[u]ncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness.”<sup>39</sup> All studies and chart reviews reported in Saggar 2014,<sup>40</sup> Agarwal 2015,<sup>41</sup> Parikh 2016,<sup>42</sup> and Faria-Urbina 2018<sup>43</sup> were uncontrolled.

71. A second source of bias associated with change scores is a subtle but important phenomenon known as “regression to the mean.” Regression to the mean is well-recognized in the art—it was described as early as 1877. “Regression to the mean is a widespread statistical phenomenon with potentially serious implications for health care. It can result in wrongly concluding that an effect is due to treatment when it is due to chance. Ignorance of the problem will lead to errors in decision making.”<sup>44</sup> It has been described as “a statistical phenomenon that can make natural variation in repeated data look like real change.”<sup>45</sup> Regression to the mean occurs

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<sup>38</sup> 21 C.F.R. § 314.126(a).

<sup>39</sup> 21 C.F.R. § 314.126(e).

<sup>40</sup> Saggar 2014.

<sup>41</sup> Agarwal 2015.

<sup>42</sup> Parikh 2016.

<sup>43</sup> Faria-Urbina 2018.

<sup>44</sup> Veronica Morton & David J Torgerson, *Effect of Regression to the Mean on Decision Making in Health Care*, 326 BMJ 1083 (2003) (“Morton & Torgerson 2003”).

<sup>45</sup> Adrian G Barnett et al., *Regression to the Mean: What It Is and How To Deal With It*, 34 Int’l J. Epidemiology 215 (2005) (“Barnett 2004”).

when patients are selected for inclusion in a clinical study because a measure of their disease severity is at an extreme. If, for example, the distance patients can walk in six minutes varies somewhat from one day to the next, then a population of patients who are selected because their 6MWD is low will include patients who happen to have a 6MWD lower than their typical average value. When those patients are measured again 12 weeks later, their 6MWD is likely to be nearer to their typical average value, and that would *appear* to be an improvement relative to that patient's baseline (even if they do not receive an effective treatment).

72. In a noncomparative, single-treatment series of cases, there is no way to know the extent to which regression to the mean is determining the extent of any observed effect. The effects of regression to the mean can be eliminated, however, by performing a comparative study in which changes observed in the active arm are compared to the corresponding changes observed in a control arm, e.g., a placebo arm.

**D. Retrospective versus prospective clinical studies**

73. Retrospective clinical studies are based on data that has already been acquired before the clinical study begins.<sup>46</sup> This means that the data were collected for a purpose other than answering the questions addressed by the retrospective clinical study. Data sources for such clinical studies include existing medical records, billing databases, and so on. Such data are often inaccurate or misleading, as patient diagnoses recorded in medical records may be incomplete and data that was collected on some patients may not have been collected on other patients. The reasons for these omissions are often unknowable but may well be associated with patients' outcomes. These studies cannot take advantage of variables that were not recorded. Relevant variables such as smoking history may be absent from the data set, and, if present, may have been collected

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<sup>46</sup> *Supra* § VII. B.

sporadically. Certain measures of disease progress may not have been carried out consistently for all patients. Referral centers specializing in treating particular diseases may have incomplete information on the medical records of patients referred to them from elsewhere. Consequently, studies based on such data sources can be subject to bias.<sup>47</sup>

74. As an example, consider a clinical study looking at change in 6MWD from initiation of treprostinil treatment to a measurement 12 weeks later. If the medical records being mined for data did not have a measurement at 12 weeks for some patients (i.e., a change in 6MWD could not be calculated for those patients), a retrospective study might simply include only those patients who have both a baseline and 12-week measurement, ignoring those patients for which 12 week data is unavailable. But there are many reasons why the 12-week measurement might be missing from the medical records being mined for data. These reasons include, but are not limited to, the following possibilities: the patient deteriorated so much in 12 weeks that they are unable to do the test; the patient developed another medical condition for which they were hospitalized at the 12-week point; the patient died; the patient was transferred to another institution for specialized treatment; the healthcare provider did not perform 6MWD test at 12 weeks; or the patient refused to do the 6MWD test at 12 weeks. I note that many of these possible reasons for the medical records not containing a patient's 12-week data could negatively impact that patient's 6MWD if the measurement had actually been taken and recorded. Therefore, only including the patients with complete 6MWD data and ignoring patients with incomplete 6MWD could give a misleading description of what happened to 6MWD in the patients initially treated with treprostinil. Incomplete follow-up in a retrospective study—like that described in the above hypothetical—

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<sup>47</sup> *Supra* § VII. B.

introduces a source of bias that cannot be corrected and that can produce substantially misleading results.

75. Prospective clinical studies—clinical studies in which criteria for inclusion in the clinical study and the outcomes to be studied are defined in advance, and patients are followed forward in time—are generally considered to produce more reliable assessments than retrospective clinical studies.<sup>48</sup> Investigators in prospective clinical studies can identify variables that are potentially important for interpreting the results, and they can ensure that those variables are measured and recorded for use in the data analysis. Because patients in a prospective clinical study are typically followed by the investigators according to a pre-specified schedule, reasons for patient dropout or the failure to record an outcome assessment can be determined and the impact of this missing data can be assessed in the final analysis.

76. Prospective clinical studies are subject to fewer types of bias than retrospective clinical studies because prospective clinical studies afford greater control over 1) what, how, and when variables related to treatment and disease are measured; 2) intensity and uniformity of follow up and outcome assessment; and 3) understanding causes of and adjusting for data gaps, e.g., subject dropout or missing data.

#### **E. Blinding versus open label**

77. In comparative clinical studies, blinding patients, healthcare providers, and investigators to the treatment assigned to each patient is a powerful guard against biases, conscious or unconscious, that arise from knowledge of a patient's treatment and which can result in favoring one treatment over another when assessing outcomes.<sup>49</sup> For example, when outcomes are based in part on a patient's self-assessments, blinding ensures that any expectations related to potential

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<sup>48</sup> *Supra* § VII. B.

<sup>49</sup> *Supra* § VII. B.

results of treatment are the same in both the active and control groups. As another example, when a patient's condition worsens during a clinical study, healthcare providers or investigators may have incentives to choose a course of action that depends upon which treatment the patient is receiving, and this choice could affect the ultimate assessment of efficacy. Blinding ensures that treatment choices during the clinical study will be unaffected by the treatment under study. Unblinded healthcare providers and investigators may also influence the outcome measure, even unconsciously, by behaving differently depending on treatment group or patient. For instance, if a healthcare provider or investigator knows that a patient is in the treprostinil group, the healthcare provider or investigator may offer extra verbal encouragement to the patient during the 6MWD test which might not be offered (or offered so vigorously) to a patient in the control group. Blinding ensures that the way assessments are carried out are unaffected by knowledge of the treatment to which individual patients are assigned.

78. Blinding is generally not feasible in single-arm studies. In retrospective studies, the investigator has chosen patients from the medical record on the basis of the common treatment that they received—in this case, inhaled treprostinil, so the investigators themselves could not be blinded. And the treating physicians of the patients in the study at least knew, and probably prescribed, the common treatment under study, so these individuals evaluating patient outcomes could also not have been blinded. In a prospective single-arm study of a treatment, all patients would receive the common treatment of interest by design.

#### **F. Sources of bias**

79. The term “bias,” as used in epidemiology and biostatistics has a technical meaning that does not imply a prejudice or preconception is at play, as in common usage.

80. In epidemiology, “[b]ias may be defined as any systematic error in an epidemiological study that results in an incorrect estimate of the association between exposure and

risk of disease.”<sup>50</sup> More generally, bias results in an incorrect estimate of the relationship between an “exposure” (such as treatment with treprostinil) and an “outcome” (such as increase in 6MWD). Bias can arise “from a large number of specific sources including the manner in which subjects are selected in the study and the way in which information is obtained, reported, or interpreted.”<sup>51</sup>

81. One particular source of bias--selection bias--occurs when the sample of patients studied--the study sample--does not fairly represent the population of patients that they are intended to represent. Selection bias can be introduced into clinical studies in a variety of ways, examples of which I outline below.

82. One type of selection bias occurs when the procedures used to identify the study sample systematically filter out some or all patients with particular characteristics. For instance, if all PH-ILD patients in a study were included because they were referred to a particular center for a lung transplant, then PH-ILD patients who were not candidates for lung transplant at that particular center would not be represented in the study sample.

83. A second type of selection bias occurs when only a subset of an initially representative study sample is analyzed. For instance, if some PH-ILD patients in a clinical study deteriorate during the clinical study to the extent that they require alternative treatment and these patients are then excluded from the analysis of the clinical study, that clinical study’s results will no longer represent what happens to PH-ILD patients in general. Rather, that clinical study’s results will only reflect those patients who happen to do well enough to complete the clinical study.

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<sup>50</sup> Hennekens CH, Buring JE. “Analysis of Epidemiologic Studies: Evaluating the Role of Bias,” Chapter 11 in *Epidemiology in Medicine*, Lippincott Williams & Wilkins, 1987, at 272. (“Hennekens & Buring 1987”).

<sup>51</sup> *Id.* at 272.

This would clearly result in an overly optimistic view of what would happen to PH-ILD patients in general.

84. A third type of selection bias can occur in comparative clinical studies when the patients who receive one treatment differ in a systematic way from those receiving a control treatment. For example, consider a nonrandomized comparative clinical study comparing outcomes for patients already receiving a pharmaceutical intervention to patients not receiving a pharmaceutical intervention. The patients already receiving a pharmaceutical intervention could well be on the drug because their disease was more advanced compared to the patients for whom it was judged that the pharmaceutical intervention would not be warranted. If one treatment group is sicker in some sense at baseline than the other, one could expect worse outcomes for that group, quite independent of their treatment.

85. Randomized assignment to treatment groups in a prospective comparative clinical study eliminates the possibility of selection bias of the third type outlined above.

**G. Randomized clinical trials**

86. The gold standard for establishing efficacy of a treatment is the multi-center, randomized, double-blind, placebo-controlled clinical trial. Such a clinical study randomly allocates participants to one of two treatments, thereby eliminating any systematic selection of patients to receive one treatment or the other. Thus, any factor (whether known or unknown) that will affect an outcome measurement will tend to be equally distributed between the two treatment arms. Moreover, double blinding reduces the possibility of bias that could result from treating patients on the active treatment differently from those on the control treatment, and it also eliminates possible bias in evaluating outcomes related to what investigators expect for the effects

of the active treatment.<sup>52</sup> Comparison to placebo controls makes it possible to eliminate any possible bias resulting from patients' or physicians' expectations and resulting psychological or psychosomatic influence on outcomes. Because patients in the active and placebo arms of the study otherwise receive the same treatment, follow-up, and evaluation throughout the study, that means that any differences in outcomes between the active and placebo arms of the study can be attributed to the only systematic difference built into the study—the difference in effectiveness of the active and placebo treatments. Finally, a study conducted across multiple institutions increases the confidence that results are not being driven by factors specific to a single investigator or an individual study site.

87. Randomized clinical trials are always prospective, and they always assess effects by comparing outcomes between patients receiving the treatment of interest and a control. Such clinical studies minimize the possibility of biases.

#### **H. Single-site clinical studies versus multi-site clinical studies**

88. Studies carried out at a single specialty clinic or referral center may not be indicative of results obtainable in a broader range of clinical settings. A specialized referral site may have standardized treatment protocols that were developed based on their experience. Clinical studies done at that site may be more likely to achieve better results than the same studies carried out at other institutions with less specialized experience.<sup>53</sup> The patients available for study at a referral center also may well differ from the patients seen at other hospitals who see patients with the disease under study. For example, patients at a referral center may reflect a population with more advanced disease.

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<sup>52</sup> *Supra* § VII. B.

<sup>53</sup> *Supra* § VII. B.

89. By way of contrast, a clinical study carried out at multiple study sites provides information about how much variability in outcomes are achieved from one location to the next. If favorable results are found broadly, that is, at most of the study sites, that fact increases confidence that clinical study's results apply generally and not just to a single, highly experienced clinic.

**I. Sample size and power**

90. Generally, an estimate for an effect (such as increase in 6MWD) based on a larger number of individuals, i.e., a larger *sample size*, is more precise than one based on a small number of individuals. Phase II clinical studies, which are typically the first studies of a drug to determine whether there are indications of efficacy, generally involve a few hundred patients.<sup>54</sup> Comparative randomized trials such as Phase III clinical trials to determine whether a drug treatment is effective typically require 100 or more patients *per treatment arm*. For example, the INCREASE trial enrolled 326 patients, with equal numbers assigned to treprostinil and to placebo.<sup>55</sup>

91. Because outcome measures can only be estimated imprecisely with small sample sizes, study results based on small samples may not be reliable indicators of results in broader populations of patients. The term “power” is a statistical term of art that refers to the ability of a particular clinical study design to detect differences (say, between a treatment and a control) of a specified size. Roughly speaking, a large clinical study has greater power to detect differences than a small clinical study.

92. The power of a clinical study depends on several factors:

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<sup>54</sup> Pedro A. Torres-Saavedra & Kathryn A. Winter, *An Overview of Phase 2 Clinical Trial Designs*, 112 Int'l J. Radiation Oncology, Biol., Physics 22 (2022) (“Torres-Saavedra & Winter 2022”).

<sup>55</sup> Aaron Waxman et al., *Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease*, 384 N. Eng. J. Med. 325 (2021) (UTC\_PH-ILD\_010790) (“Waxman 2021”) at 790.

- The sample size,<sup>56</sup>
- The degree of variability from one patient to another and from one measurement to another in the quantity being measured,
- The details of the clinical study design, including what specific comparison will be made,<sup>57</sup>
- The specific statistical test to be used,<sup>58</sup> and
- The size of the (average) difference that one seeks to detect.

93. Generally, clinical studies with larger samples have greater power. Larger inter-patient and inter-measurement variability results in lower power. Certain statistical tests have greater power than others for testing the same difference; which tests have greatest power depends on characteristics of the sampling method by which observations are taken.

#### **J. Statistical significance**

94. A statistical significance test is a formal comparison of an observed effect against a benchmark for comparison. In an uncontrolled single-arm clinical study, for example, a significance test could be used to compare the average change in 6MWD in the sample subjects to the benchmark of zero, that is, no change. In a randomized clinical trial, for example, a significance test could be used to compare the average change in 6MWD in subjects receiving treprostinil to the average change in 6MWD in subjects receiving placebo.

95. For most statistical tests, the results can be summarized in a quantity called the p-value, a numerical quantity ranging between 0 and 1. P-values close to 1 result when the observed

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<sup>56</sup> *Supra* § VII. B.

<sup>57</sup> *Supra* § VII. B.

<sup>58</sup> *Supra* § VII. B.

effect is close to the benchmark comparison value, while p-values closer to 0 result when the observed effect and the benchmark diverge.

96. By convention, when the p-value is less than 0.05, the observed difference in means is said to be “statistically significantly different from zero.” This cumbersome phrase is often simply abbreviated as “statistically significant.” Note that the terms “statistical significance” and “statistically significant” are statistical terms of art that always refer to the results of a specific statistical test of a specific comparison carried out on a specific data set derived from a specific study design.

97. The p-value is the result of a statistical computation that depends upon (a) the size of the observed effect (for example, a difference between two treatment regimens), (b) the degree of variability in the measurement of those effects, (c) the number of patients involved in the comparison, and (d) the specifics of how the data were collected. The p-value is expressed on a scale from zero to one. Smaller p-values, that is, those closer to zero, are considered to be “more significant.” A statistically significant result comparing the effects of two treatments, one of which may be a placebo or control treatment, (i.e., the p-value being  $<0.05$ ) will occur no more often than one time in twenty if there were, in fact, no actual differences in those treatments’ effects.

98. The term “statistical significance” is often applied as a descriptive term in nonrandomized or noncomparative clinical studies to denote that a statistical calculation resulted in a p-value less than 0.05. Because there is no chance mechanism (such as randomization) in such studies, the usual interpretation of the p-value in that context is problematic.

99. Small p-values are commonly said to indicate that the difference between the measured effect and the benchmark are likely not “due to chance.” The role of chance, and the interpretation of a statistically significant result, depend upon the design of the clinical study, as

well as the specific statistical test employed. The paragraphs below discuss significance tests in the context of two specific types of clinical study design.

**1. Comparisons against baseline in a single-arm clinical study**

100. In a single-arm clinical study in which the outcome of interest is the difference between an endpoint's baseline value and its value at a later point in time is calculated, the term "statistical significance" means that the average difference is sufficiently large that an average difference of zero—that is, no change from baseline—cannot plausibly be attributed to inter-patient variability.

101. If the average change is statistically significantly different from zero, one cannot conclude that treatment received by the patients accounts for some or all the change. While such a finding would be consistent with such an explanation, the finding is also compatible with many other explanations. Indeed, it is possible that comparable changes would have occurred in patients who did *not* receive the treatment.

102. One possible alternative explanation is the phenomenon of regression to the mean, discussed above.<sup>59</sup> Another possible alternate explanation is omission of patients from the study who are deemed unlikely to improve. A third possible alternate explanation is the natural course of the disease process. A fourth possible alternative explanation is change caused by other aspects of treatment received by all patients at the same time as the common treatment of interest. Eliminating the possibility of all of these alternative explanations can only begin to be achieved by conducting a comparative study.<sup>60</sup>

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<sup>59</sup> *Supra* § VII. C.

<sup>60</sup> *Supra* § VII. B.

**2. Comparisons against a placebo control in a randomized clinical trial**

103. When comparing two treatment arms from a randomized clinical trial, the term “statistical significance” means that the data used in the test, standing by themselves, exhibit differences between the treatments that are sufficiently great that they cannot plausibly be attributed to chance.

104. As discussed above, the only systematic difference between the two treatment arms in a randomized clinical trial is the difference in the treatments—any other possible factors that could affect the outcome have been distributed with equal probability to the two groups. Put differently, if the role of chance can be ruled out as accounting for an observed difference because of the random procedure that assigned some patients to treatment A and others to treatment B, it follows that the only other explanation for the observed difference is the single systematic difference between the groups, that is, the difference in outcome is due to the difference between the two treatments.

105. The larger the true difference in average response to the two treatments, the greater the chance that a statistical test will attain statistical significance. That is, the statistical test has greater power to detect larger differences than smaller ones.<sup>61</sup> Similarly, the larger the sample size in each group, the greater the power the statistical test will have to detect differences between the groups.

**K. Clinicaltrials.gov**

106. Clinicaltrials.gov is a searchable registry of clinical studies. The site is maintained by the National Library of Medicine. Clinical study sponsors register certain information regarding

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<sup>61</sup> “Detecting a difference” in this context means producing data which results in a difference that is statistically significant, that is, that produces a p-value less than 0.05.

their clinical studies in advance of identifying all study centers, recruiting patients, initiating treatments, following patient outcomes, carrying out statistical analyses, and reporting results. As the stages in executing the study is carried out, these additional elements are added to the ClinicalTrials.gov database and website as date-stamped versions, all of which are publicly available as of the date of posting. The information may include the clinical study's inclusion and exclusion criteria, what question(s) the clinical study intends to answer, what outcomes will be measured, plans for how the clinical study will be carried out, and the analyses proposed to answer the questions of interest. When a clinical study is completed, results of the clinical study can be added to the database.

107. Pre-registration of a study on clinicaltrials.gov ensures that the outcomes to be studied are defined and made public in advance, so that it will be clear how the clinical study will go about using the data collected to answer the question of interest. At the pre-registration stage, no data have been collected, and no conclusion or prediction about the outcome of the clinical study can be made based on the registered clinical study design.

108. Modifications to a clinical study, such as adding results or documenting changes to the study protocol, are logged and dated in the archive, so the status of what had been posted and made public at any given point in time can be identified.

## **VIII. THE '327 PATENT**

109. The '327 patent relates to the treatment of PH-ILD using inhaled treprostinil. Specifically, the '327 patent claims methods of improving exercise capacity in a patient suffering from PH-ILD by administering an effective amount of inhaled treprostinil. The application for the '327 patent was filed on April 16, 2021, and claims priority to provisional applications 63/011,810 and 63/160,611, filed on April 17, 2020 and March 12, 2021, respectively.

110. The named inventors are Leigh Peterson, Peter Smith, and Chunqin Deng.

111. The '327 patent has 19 claims, including 1 independent claim and 18 dependent claims, all of which are reproduced below.

1. A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath.
2. The method of claim 1, wherein said administering provides a statistically significant increase of a 6 minutes walk distance in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.
3. The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks of the administering.
4. The method of claim 1, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.
5. The method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.
6. The method of claim 1, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.
7. The method of claim 1, wherein said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease.
8. The method of claim 7, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.
9. The method of claim 1, wherein said administering provides a statistically significant improvement of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering.
10. The method of claim 9, wherein said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.
11. The method of claim 1, wherein said administering is performed by a pulsed inhalation device.

**12.** The method of claim 11, wherein the pulsed inhalation device contains an inhalation solution comprising treprostinil or a pharmaceutically acceptable salt thereof.

**13.** The method of claim 11, wherein the pulsed inhalation device is a nebulizer.

**14.** The method of claim 11, wherein the pulsed inhalation device is a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof.

**15.** The method of claim 1, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15 µg to 100 µg.

**16.** The method of claim 15, wherein the single inhalation administration event does not exceed 15 breaths by the patient.

**17.** The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks of the administering.

**18.** The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 12 weeks of the administering.

**19.** The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 16 weeks of the administering.

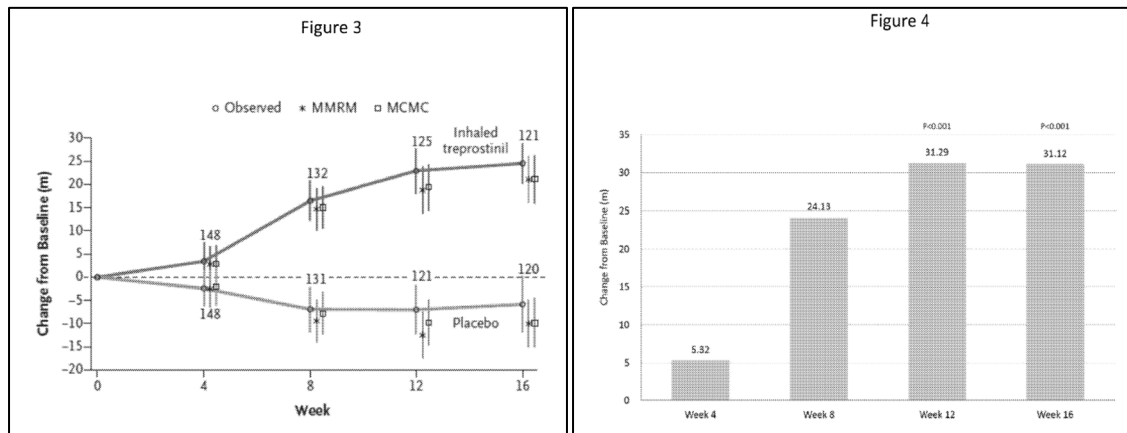
112. Claim 1 describes a method “for improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease,” and each of dependent claims 2–7, 9–10, and 17–19 claims a method that increases, or provides an increase of, or provides a reduction, improves, or provides an improvement in a particular clinical outcome. Improvements can only be attributed to practicing the claimed method if they exceed any improvements that result from *not* practicing the method.

113. In the '327 patent's specification, Examples 1 and 3 describe statistically significant reduction in number of exacerbations, decrease in risk of exacerbation, improved FVC parameters, increased 6MWD, and reduced plasma NT-proBNP, among other clinical outcome measures. *All of these assessments of statistical significance of improvements are based on comparisons of inhaled treprostinil to placebo.* This fact, coupled with the fact that the specification describes no

“statistically significant” changes from baseline based only on PH-ILD patients receiving inhaled treprostinil, confirms my assessment that the claims concerning improvements (as well as increases or reductions) all refer to improvements relative to a placebo control.

114. I understand that the specification of the '327 patent reports key data from UTC's groundbreaking INCREASE clinical trial, discussed in detail below.<sup>62</sup>

115. The data reported in the specification demonstrates that administration of treprostinil according to the claimed methods of treatment resulted in a statistically significant improvement in exercise capacity compared to placebo treatment among PH-ILD patients as measured by the 6MWD test.<sup>63</sup> Figures 3 and 4 of the '327 patent, reproduced below, depict these 6MWD results as a function of time.<sup>64</sup> In the aggregate, patients receiving inhaled treprostinil exhibited an improvement at the very first measurement point in 6MWD that grew steadily over the 16-week course of treatment while patients receiving placebo exhibited a gradual and continuing decline in 6MWD over the same period.<sup>65</sup>



<sup>62</sup> See generally '327 patent at 26:27–45:20 (Example 3); '327 patent at 28:10–14 (identifying trial as “INCREASE”); '327 patent at Table 5 (6MWD results), '327 patent at tbl. 10 (FVC results).

<sup>63</sup> *Id.* at 26:57–61; 27:7–10; 32:39–45; 35:42–44; tbl. 5.

<sup>64</sup> *Id.* at fig. 3, fig. 4, 4:42–5:9.

<sup>65</sup> *Id.*

116. Furthermore, the data reported in the specification of the '327 patent demonstrates that the claimed methods resulted in fewer exacerbations due to the interstitial lung disease and clinical worsening events due to the interstitial lung disease, improvements for many patients in FVC, and reduced NT-proBNP levels in blood plasma.<sup>66</sup>

117. Dr. Channick's report frequently cites to materials, e.g., depositions from this litigation, in its treatment of the '327 patent.<sup>67</sup> Because these materials would not have been available to the POSA these materials do not support Dr. Channick's positions.

## **IX. ALLEGED PRIOR ART DISCLOSURES REGARDING INHALED TREPROSTINIL IN PULMONARY HYPERTENSION SUBJECTS**

118. Dr. Channick's expert report identifies several alleged prior art references to support his view that the method of treatment claimed by the '327 patent would have been obvious to a POSA as of the priority date. I have been asked to review those references and opine regarding how the POSA would evaluate and view the data disclosed therein and the appropriate conclusions, if any, that can be drawn from the data. As explained in more detail on a reference-by-reference basis below, it is my opinion that none of the references asserted by Dr. Channick would suggest to the POSA as of the priority date that inhaled treprostinil has demonstrated a robust treatment effect on exercise capacity in PH-ILD patients.

### **A. The '793 Patent**

119. U.S. Patent No. 10,716,793 ("793 patent") is titled "Treprostinil Administration By Inhalation" and was issued by the Patent and Trademark Office on July 21, 2020. The '793 patent is directed to "therapeutic methods involving administering treprostinil using a metered

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<sup>66</sup> *Id.* at 22:45–50, 26:65–27:3; 33:45–34:36; 35:25–30; 35:47–49; tbl. 5; fig. 1 (exacerbations and clinical worsening); 25:24–43; tbls. 1–3 (FVC); 26:61–65; 33:38–45; 35:44–47 (NT-proBNP).

<sup>67</sup> Channick Op. Rept. ¶¶ 78, 83–84.

dose inhaler and related kits.”<sup>68</sup> I reviewed the ’793 patent and did not see any data reporting improved exercise capacity in PH-ILD patients.

120. Dr. Channick has asserted that “the ’793 patent claims a method of treating PH-ILD patients with inhaled treprostinil and improving their exercise capacity.”<sup>69</sup> Dr. Channick has also asserted that a POSA “would have understood that pulmonary fibrosis as described in the ’793 patent is a form of PH-ILD, and that PH-ILD patients were treated in the ’793 patent examples.”<sup>70</sup> As mentioned above and described in more detail below, I disagree with his conclusions.

121. Example 1 of the ’793 patent discloses an “Open Label Study Upon Acute Safety, Tolerability and Hemodynamic Effects of Inhaled Treprostinil Delivered in Second.”<sup>71</sup> The study included 45 patients with moderate to severe precapillary pulmonary hypertension.<sup>72</sup> Specifically, the disease etiologies that were included in the study were idiopathic PAH (n=13), PAH other (n=11), chronic thromboembolic pulmonary hypertension (n=17), and pulmonary fibrosis (n=4).<sup>73</sup> Thus, only 4 of the 45 patients had a pulmonary fibrosis disease etiology. The patient characteristics of the various treatment groups that were evaluated in the study are reproduced in the table below.

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<sup>68</sup> ’793 patent at 1:21-23.

<sup>69</sup> Redacted Version of 2024-12-20 Expert Report of Dr. Richard Channick (“Channick Op. Rept.”) at ¶ 229.

<sup>70</sup> Channick Op. Rept. at ¶ 237.

<sup>71</sup> ’793 patent at 8:56-11:67.

<sup>72</sup> *Id.* at 9:36-49.

<sup>73</sup> *Id.*

'793 Patent, Table 1<sup>74</sup>

TABLE 1				
Patient characteristics of the different treatment groups. Data are given as mean $\pm$ Standard Error of the Mean (SEM).				
	Placebo (n = 4)	30 $\mu$ g TRE (n = 12)	45 $\mu$ g TRE (n = 9)	60 $\mu$ g TRE (n = 20)
Age [years]	61 $\pm$ 8	53.9 $\pm$ 3.9	54.2 $\pm$ 5.7	65.5 $\pm$ 3.1
PAP [mmHg]	49.5 $\pm$ 10.1	45 $\pm$ 3.1	54.3 $\pm$ 2.8	39.7 $\pm$ 2.0
PVR [Dynes]	896 $\pm$ 163	597 $\pm$ 53.9	1049 $\pm$ 107	663 $\pm$ 81
CO [l/min]	4.46 $\pm$ 0.9	5.2 $\pm$ 0.4	3.9 $\pm$ 0.4	4.4 $\pm$ 0.3
SAP [mmHg]	98 $\pm$ 8.1	90.1 $\pm$ 3.2	82.8 $\pm$ 3.9	86.1 $\pm$ 2.0
SaO <sub>2</sub> [%]	85.3 $\pm$ 4.5	90.0 $\pm$ 1.1	89.6 $\pm$ 1.1	90.6 $\pm$ 0.5
SvO <sub>2</sub> [%]	57.5 $\pm$ 3.9	66.0 $\pm$ 1.6	59.1 $\pm$ 3.4	62.5 $\pm$ 1.6
PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; SaO <sub>2</sub> = arterial oxygen saturation; SvO <sub>2</sub> = central venous oxygen saturation.				

122. The specification of the '793 patent explains that “[h]eart rate, pulmonary and systemic blood pressure and cardiac output were measured and blood gases were taken during each pharmacological intervention at defined time points.”<sup>75</sup> The study demonstrated that “[t]reprostinil is tolerated at high doses with no systemic side effects” and that “[t]he application of an effective amount of treprostinil in only few or even one single breath was achieved with a highly concentrated treprostinil sodium solution.”<sup>76</sup> The underlying hemodynamic and gas exchange results, which are reproduced in the table below, were reported based on aggregated data for all disease etiologies that were evaluated in the study. In other words, Example 1 does not report any hemodynamic or gas exchange data that is specific to the subgroup of patients with a pulmonary fibrosis disease etiology.

<sup>74</sup> *Id.* at 9:50-65.

<sup>75</sup> *Id.* at 9:67-10:3.

<sup>76</sup> *Id.* at 62-66.

'793 Patent, Table 2<sup>77</sup>

TABLE 2				
Extremes of the relative changes of hemodynamic and gas exchange parameters compared to baseline after inhalation of Placebo (n = 4), 30 µg treprostinil (n = 12), 45 µg treprostinil (n = 9) and 60 µg treprostinil (n = 20). Highest (max) and lowest (min) values during the observation period are shown. Data are given as percent of baseline values (mean ± SEM).				
	Placebo	30 µg TRE	45 µg TRE	60 µg TRE
PAP (min)	99.4 ± 3.0	83.4 ± 3.2	77.6 ± 6.8	79.5 ± 2.4
PVR (min)	101.4 ± 1.9	84.4 ± 4.4	71.4 ± 8.9	77.5 ± 3.7
CO (max)	99.7 ± 1.1	108.8 ± 3.8	108.6 ± 5.6	103.8 ± 2.0
SVR (min)	104.3 ± 4.3	97.7 ± 4.2	92 ± 3.9	91.3 ± 2.1
SAP (min)	102.7 ± 1.7	97.3 ± 1.9	96.1 ± 1.5	93.6 ± 2.9
HR (max)	105 ± 2.1	106.1 ± 2.9	99.1 ± 2.4	101.1 ± 0.9
SaO <sub>2</sub> (min)	98.2 ± 0.4	101 ± 0.3	94.4 ± 1.8	95.8 ± 0.9
SvO <sub>2</sub> (max)	104.5 ± 1.4	102.4 ± 1.3	104.5 ± 4.4	102 ± 1.0

PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; HR = heart rate; SaO<sub>2</sub> = arterial oxygen saturation; SvO<sub>2</sub> = central venous oxygen saturation.

123. In addition, the study described in Example 1 also analyzed 5 patients to determine whether the inhalation of highly concentrated aerosol would lead to “increased shunt flow” or “increase of low ventilation/perfusion.”<sup>78</sup> This analysis only included 1 patient with pulmonary fibrosis disease etiology.<sup>79</sup> Similar to the results described above, the results here were reported in the aggregate and without specific reference to the single patients with pulmonary fibrosis disease etiology.

124. Example 2 of the '793 patent discloses an “Investigation of the Effects of Inhaled Treprostinil on Pulmonary Hemodynamics and Gas Exchange in Severe Pulmonary Hypertension.”<sup>80</sup> This investigation details three different studies that were conducted on 123 patients by means of right heart catheterization: (1) the first study was a randomized crossover-

<sup>77</sup> *Id.* at 11:9-28.

<sup>78</sup> *Id.* at 11:34-60.

<sup>79</sup> *Id.*

<sup>80</sup> *Id.* at 12:1-18:20.

design study with 44 patients, (2) the second was a dose escalation study with 31 patients, and (3) the third was a study of reduction of inhalation time while keeping the dose fixed with 48 patients.<sup>81</sup> The primary objectives across the studies were, respectively, “to compare the acute hemodynamic effects and the systemic side effects of inhaled treprostinil with inhaled iloprost at comparable doses”; “to describe the pharmacodynamic and pharmacokinetic effects of inhaled treprostinil at a well tolerated dose (30 µg) and to explore the highest tolerated single dose”; and “to explore the shortest possible inhalation time for a 15 µg dose of inhaled treprostinil.”<sup>82</sup> The disease etiologies of the pulmonary hypertension patients included in the studies, along with the results of various pulmonary function testing, are detailed in the table below.

**’793 Patent, Table 3<sup>83</sup>**

	N	Age	Gender f/m	Etiology i/o/t/f	PAP [mmHg]	PVR [dyn * s * cm <sup>-5</sup> ]	SAP [mmHg]	CVP [mmHg]	PAWP [mmHg]	CO [l/min]	SaO <sub>2</sub> [%]	SvO <sub>2</sub> [%]
1a	14	55.1 ± 4.8	11/3	4/4/2/4	53.8 ± 3.1	911 ± 102	95.4 ± 3.6	7.4 ± 1	8.0 ± 0.8	4.3 ± 0.4	93.8 ± 2	63.9 ± 2.4
1b	14	54.1 ± 3.3	10/4	1/6/5/2	47.4 ± 3.8	716 ± 80	90.6 ± 3.3	5.9 ± 1.4	6.4 ± 0.7	4.7 ± 0.4	92 ± 1	64.4 ± 2.3
1c	16	56 ± 2.9	7/9	6/3/6/1	47.5 ± 4.5	777 ± 102	92 ± 4.5	8.3 ± 1.4	8.6 ± 1.4	4.4 ± 0.5	91.4 ± 0.9	59.8 ± 2.6
2a	8	60.8 ± 4	4/4	2/2/3/1	51.9 ± 4.9	849 ± 152	95.9 ± 4.8	7.6 ± 1.4	11.1 ± 1.7	4.4 ± 0.6	89.6 ± 2.8	60.1 ± 2.8
2b	8	52.8 ± 6.6	6/2	1/3/3/1	49 ± 4	902 ± 189	92.4 ± 2.4	4.8 ± 1.1	7.2 ± 1.3	4.0 ± 0.4	92.4 ± 2.4	62.5 ± 1.7
2c	6	56.8 ± 5.9	4/2	0/2/2/2	44.2 ± 3.5	856 ± 123	96.3 ± 3.9	5 ± 1.1	6 ± 1	3.8 ± 0.3	92.8 ± 1.5	63.6 ± 1.8
2d	6	51.2 ± 3.8	4/2	2/2/2/0	55.5 ± 4.9	940 ± 110	91.2 ± 8.1	11.2 ± 1.2	10 ± 0.7	3.9 ± 0.4	92 ± 1.9	62 ± 5.8
2e	3	57.3 ± 9.1	1/2	0/1/0/2	45.3 ± 5.2	769 ± 267	99 ± 3.2	5 ± 2.1	9 ± 0.6	4.5 ± 0.6	94.2 ± 1.3	66.3 ± 1.5
3a	6	52.7 ± 6.6	4/2	2/4/0/0	53.8 ± 6.7	928 ± 145	92.7 ± 7.9	8.7 ± 2.7	8.8 ± 1.3	4.2 ± 0.6	90.4 ± 2.8	64.8 ± 4.3
3b	6	58.3 ± 3.5	4/2	3/1/1/1	54.2 ± 6.1	808 ± 156	94.3 ± 2.8	7 ± 1.4	10 ± 1.3	5 ± 0.7	91.9 ± 0.7	63.5 ± 2.9
3c	21	57.4 ± 5.6	8/3	7/7/6/1	46.1 ± 2.5	900 ± 99	88 ± 2.8	9 ± 1.4	9.2 ± 0.5	3.7 ± 0.3	91.7 ± 0.5	59.7 ± 2
3d	7	55.6 ± 5.8	3/4	0/4/3/0	53.1 ± 7.1	732 ± 123	91.4 ± 5.6	7.9 ± 3.1	8.6 ± 1.3	5 ± 0.4	90.7 ± 1.4	61.3 ± 3.7
3e	8	59 ± 5.2	7/1	0/4/4/0	45.1 ± 3.9	733 ± 114	92.8 ± 6.8	4.6 ± 0.8	8.1 ± 1.1	4.3 ± 0.2	90.7 ± 0.8	66.3 ± 2.8

Group 1 corresponds to study i); randomized crossover study comparing inhaled iloprost (ILO) and inhaled treprostinil (TRE).  
a = 7.5 g ILO vs. 7.5 µg TRE,  
b = 7.5 g ILO vs. 15 µg TRE (6 min inhalation time),  
c = 7.5 g ILO vs. 15 µg TRE (3 min inhalation time).  
Group 2 corresponds to study ii); evaluation of maximal tolerated dose of TRE.  
a = placebo inhalation,  
b = 30 µg TRE,  
c = 60 µg TRE,  
d = 90 µg TRE,  
e = 120 µg TRE.  
Group 3 corresponds to study iii); reduction of inhalation time by increase of TRE concentration, aiming at a total inhaled dose of 15 µg.  
a = 18 pulses of 100 µg/ml TRE,  
b = 9 pulses of 200 µg/ml TRE,  
c = 3 pulses of 600 µg/ml TRE,  
d = 2 pulses of 1000 µg/ml TRE,  
e = 1 pulse 2000 µg/ml TRE.  
Etiology of pulmonary hypertension was classified as idiopathic PAH (i), PAH of other causes (o), chronic thromboembolic PH (t), and pulmonary fibrosis (f).

<sup>81</sup> *Id.* at 12:20-27.

<sup>82</sup> *Id.* at 12:61-64, 13:52-55, 13:66-14:33.

<sup>83</sup> *Id.* at 13:1-14:32.

125. Thus, as explained above with respect to Example 1, Example 2 does not make any specific reference to the improvement of any hemodynamic parameter on a patient-specific basis, let alone for PH-ILD patients. The examples of the '793 patent specification contain only aggregated data for pulmonary hypertension patients with various disease etiologies, and a POSA would not understand from such disclosures any specific treatment effect for patients with a pulmonary fibrosis disease etiology.

126. Dr. Channick's report frequently cites to materials, e.g., depositions from this litigation, in its treatment of the '793 patent.<sup>84</sup> Because these materials would not have been available to the POSA these materials do not support Dr. Channick's positions.

**B. Saggar 2014**

127. Saggar 2014 reports a prospective, single-center, single-arm, open-label study of 15 outpatient lung-transplant (LT) candidates purportedly presenting with pulmonary fibrosis and advanced pulmonary hypertension, defined as mean pulmonary artery pressure (mPAP)  $\geq 35$  mm Hg, pulmonary artery wedge pressure (PAWP)  $\leq 15$  mm Hg, and pulmonary vascular resistance (PVR)  $> 240$  dyn s/cm (i.e., 3 WU).<sup>85</sup> Saggar 2014 reports that the following were excluded from the study population: other pulmonary hypertension etiologies; sarcoidosis and systemic sclerosis spectrum of disease; and patients requiring  $>10$  L/min of oxygen at baseline.<sup>86</sup> Patients with combined pulmonary fibrosis emphysema (CPFE) were included.<sup>87</sup> Threshold measures of right heart size or function were not required for study enrollment.<sup>88</sup> Formal pulmonary rehabilitation was not prescribed during the study period.<sup>89</sup> Subjects were permitted to remain on background

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<sup>84</sup> Channick Op. Rept. ¶¶ 114, 222, 226.

<sup>85</sup> Saggar 2014 at 00000226 to 00000227, abstract.

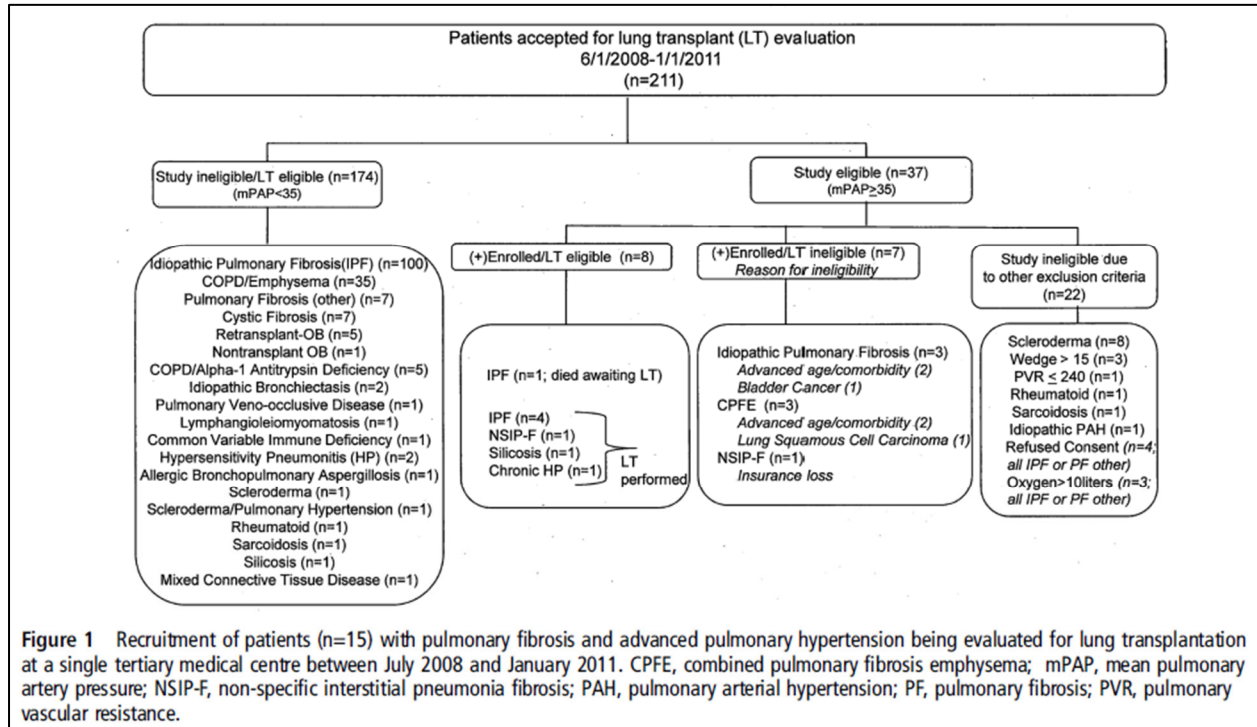
<sup>86</sup> *Id.* at 00000227.

<sup>87</sup> *Id.*

<sup>88</sup> *Id.*

<sup>89</sup> *Id.*

pulmonary fibrosis therapy, and it appears that patients were also permitted to remain on their background pulmonary-hypertension-targeted therapies.<sup>90</sup> Sagar 2014 diagrams disposition as follows:<sup>91</sup>



128. Sagar 2014 reports that all patients were administered treprostinil via parenteral administration, either intravenously or subcutaneously, at a rate of 2 ng/kg/min initially, with subsequent increases in dosage every 12 hours in the hospital, and every 2–3 days after discharge.<sup>92</sup> Dosing was limited by individual adverse reactions.<sup>93</sup> The study had no control treatment.<sup>94</sup> Prespecified endpoints were changes (from baseline to 12 weeks) in hemodynamics, echocardiography, dyspnea, quality of life assessment, and 6MWD. Measurement procedures for the endpoints were detailed in advance and uniformly applied. The open-label study was conducted

<sup>90</sup> *Id.*

<sup>91</sup> *Id.*

<sup>92</sup> *Id.* at 00000237.

<sup>93</sup> *Id.*

<sup>94</sup> *Id.* at 00000231.

at a single site, UCLA.<sup>95</sup> Saggar 2014 describes this site as a tertiary medical center—which is a site that offers high specialized equipment and expertise.<sup>96</sup> Subjects were recruited between July 2008 and January 2011.<sup>97</sup>

129. The authors also explicitly note that arterial blood gas (“ABG”) measurements were not taken during the study, and that the absence of ABG testing was a limitation impacting their conclusions concerning hypoxaemia.<sup>98</sup> Specifically, the Saggar 2014 authors explain that treating PF patients with severe PH “raises concern for ... hypoxaemia” and that they “surmise that a gentler uptitration of parenteral prostanoid, as employed in our study PF population with advanced PH, may lessen the potential for ... hypoxaemia.”<sup>99</sup> Saggar 2014 also concluded that “[t]he combined observations of improved right heart function and stable arterial oxygen saturation in our PF-PH cohort after chronic parenteral treprostinil suggests the advanced PH phenotype may be critical when considering PH-targeted therapy, as it lends itself towards ... decreased risk of hypoxaemia.”<sup>100</sup> However, Saggar 2014 indicates that ABG would have allowed the authors to confirm that “pulmonary function (i.e., degree of PH) remained unaltered during the study and likely did not confound” their findings that there was not significant hypoxaemia.<sup>101</sup>

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<sup>95</sup> *Id.* at 00000227.

<sup>96</sup> *Id.* at 00000227; *Tertiary Healthcare*, NATIONAL LIBRARY OF MEDICINE SUBJECT HEADINGS THESAURUS (2024), available at <https://meshb-prev.nlm.nih.gov/record/ui?ui=D063128> (“Care of a highly technical and specialized nature, provided in a medical center, usually one affiliated with a university, for patients with unusually severe, complex, or uncommon health problems.”); *Tertiary Care Centers*, NATIONAL LIBRARY OF MEDICINE SUBJECT HEADINGS THESAURUS (2024), available at <https://meshb-prev.nlm.nih.gov/record/ui?ui=D062606> (“A medical facility which provides a high degree of subspecialty expertise for patients from centers where they received SECONDARY CARE”).

<sup>97</sup> *Id.* at 00000227.

<sup>98</sup> *Id.* at 00000230, 00000231.

<sup>99</sup> *Id.* at 00000231.

<sup>100</sup> *Id.*

<sup>101</sup> *Id.* at 00000230.

The potential for worsening gas exchange with PH-targeted therapy deserves particular attention. We did not appreciate any significant hypoxaemia as assessed by PPO after treprostinil therapy, either at rest or after 6MWD testing. Importantly, pulmonary function (i.e., degree of PF) remained unaltered during the study and did not likely confound these findings. Although arterial blood gases (ABG) were not obtained to confirm this finding, we can suggest a rationale based on the available literature.

130. In other words, the Saggar 2014 authors acknowledge that their conclusion concerning a potential negative effect of the treatment—worsening gas exchange or hypoxaemia—may have been confounded by pulmonary function, but that this could not be confirmed because they did not measure ABG during the study.

131. Because the study reported in Saggar 2014 was an open-label, single-arm study,<sup>102</sup> that study is by definition neither randomized, blinded, nor placebo-controlled.<sup>103</sup>

**1. Saggar 2014 study design imposes significant limitations on findings, some of which are explicitly recognized.**

132. The study reported by Saggar 2014 is subject to numerous limitations discussed in Section VII above, including those associated with studies that are single-center; have a single-arm and are thus uncontrolled and nonrandomized; have a small sample size; have an unrepresentative sample subject to selection bias; include patients on variable background therapies; examine change-score outcomes; and are open-label.<sup>104</sup>

133. In particular, all comparisons are made between individual patients' baseline and the 12-week endpoint.<sup>105</sup> Such change scores are at least subject to the potential biases outlined above.<sup>106</sup> Importantly, tests of statistical significance in change scores in patients, all of whom

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<sup>102</sup> *Id.* at 00000226 to 00000227.

<sup>103</sup> *Supra* § VII.

<sup>104</sup> *Supra* § VII.

<sup>105</sup> Saggar 2014 at 00000230, Table 4.

<sup>106</sup> *Supra* § VII.

have received the same treatment under study—here, parenteral treprostinil—*cannot* be used to draw inferences about the effectiveness of that treatment.<sup>107</sup>

134. The Saggar 2014 authors identify a number of limitations, including “the heterogeneity of the pulmonary fibrosis population, variable background pulmonary-hypertension-targeted therapy, and the absence of arterial blood gas testing.”<sup>108</sup> The authors expressly identify the “absence of a placebo arm [as] a particularly significant limitation.”<sup>109</sup> I agree. As I explain in Section VII, the absence of a placebo control severely limits a study, as investigators cannot draw conclusions about the effectiveness of the treatment without comparison to a suitable control.<sup>110</sup> The authors also expressly acknowledge that their “findings must be confirmed with a randomized, placebo-controlled trial” because their study lacks a placebo control.<sup>111</sup> I agree, but I also note that the authors do not go far enough, overlooking the need to blind their proposed next study and to expand to multiple centers.

135. Immediately after the authors declare that the absence of a placebo control was a particularly significant limitation of their data, they also conclude:

At this point, the routine use of PH-targeted therapy in PF-PH is not recommended and should only be cautiously considered at specialized PH centres to avoid the serious potential for worsening cardiopulmonary status in this patient population.<sup>112</sup>

136. Assuming this recommendation reflects the standard of care for these patients when this data was reported, I agree that in no way do the reported data demonstrate a treatment effect justifying any deviation from this standard of care, especially absent significant further testing,

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<sup>107</sup> *Supra* § VII.

<sup>108</sup> Saggar 2014 at 00000231.

<sup>109</sup> *Id.*

<sup>110</sup> *Supra* § VII.

<sup>111</sup> *Supra* § VII.

<sup>112</sup> Saggar 2014 at 00000231.

e.g., at least the randomized, placebo-controlled trial the authors expressly recommend (although I believe such a study would also need to be blinded and multi-center).

**2. Saggar 2014 study suffered from severe selection bias and small sample size.**

137. Considering that the study reported by Saggar 2014 only involved 15 patients, it is subject to limitations associated with low sample size.<sup>113</sup> For example, such a small sample in and of itself strongly indicates that the data reported by Saggar 2014 may be unrepresentative of PH-ILD patients.

138. Moreover, the 15-patient cohort appears to represent a very select subset of PH-ILD patients, in that all participants had to have been referred to UCLA's tertiary site for lung transplantation evaluation.<sup>114</sup> I note that the criteria for referral are not described and could well vary from patient to patient. Consequently, at least for these reasons, it is unclear how the data reported by Saggar 2014 would apply to the broader population of PH-ILD patients.

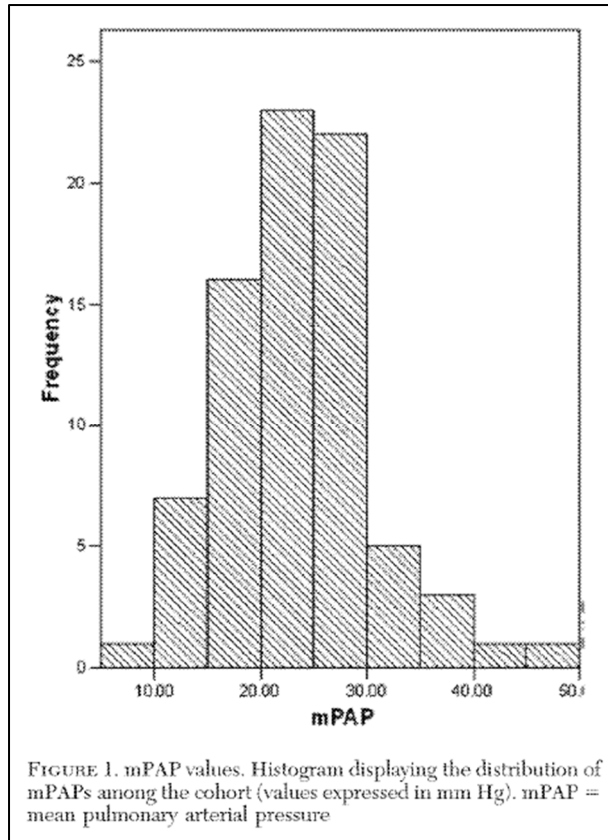
139. Additionally, the patients studied in Saggar 2014 were required to have "advanced" pulmonary hypertension (mPAP  $\geq$  35 mm Hg; PAWP  $\leq$  15 mm Hg; and PVR  $>$  240 dyn s/cm). I understand that PH-ILD patients with mPAP  $\geq$  35 mmHg is only a subset of all PH-ILD patients<sup>115</sup>:

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<sup>113</sup> *Id.* at 00000227, abstract.

<sup>114</sup> *Id.* at 00000230.

<sup>115</sup> Christopher J. Lettieri et al., *Prevalence and Outcomes of Pulmonary Arterial Hypertension in Advanced Idiopathic Pulmonary Fibrosis*, 129 *Chest* 746 (2006) (UTC\_PH-ILD\_020775) ("Lettieri 2006") at -778, Fig. 1. ("Lettieri 2006").



140. Thus, Saggat 2014 does not establish with even a minimal degree of certainty how results from this study would apply to the broader population of PH-ILD patients.

141. Another limitation of Saggat 2014 is that treprostinil is administered parenterally—that is, by intravenous or subcutaneous infusion. This route of administration differs from that described in the '327 patent, in which the method claimed requires administration by inhalation. Good biostatistical practices generally require studying a given drug for efficacy in the same route of administration about which conclusions are desired.

### 3. Saggat 2014's cautionary conclusions in view of its limitations.

142. In view of the limitations noted above,<sup>116</sup> the authors' conclusion that their findings "are only hypothesis generating and require confirmation in a multi-centre, randomized study

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<sup>116</sup> *Supra* § IX. B. 1, 2.

design” is warranted.<sup>117</sup> Because the study involved only 15 patients selected from a narrowly-defined subset of PH-ILD patients (“an advanced PH phenotype”) and no placebo control for comparison, any changes, including those reported for 6MWD and BNP levels, cannot be attributed unambiguously to parenteral administration of treprostinil.<sup>118</sup>

143. I note that the authors’ conclusion “that gradual initiation and chronic parenteral treprostinil *may* improve hemodynamics and right heart function without compromising systemic oxygenation” is uncertain—“may”—and is restricted to the studied group (patients with an advanced PH phenotype and right ventricular dysfunction).<sup>119</sup> The authors further conclude that the reported improvements in hemodynamics and right heart function without compromised systemic oxygenation are “only hypothesis generating and require confirmation in a multicentre, randomised study design.”<sup>120</sup> I agree, but the authors also overlook the need for their “required” further study be a blinded one.

144. In the “Conclusion” section, the authors do not appear to draw any clinical conclusions with respect to the reported 6MWD or BNP findings. Indeed, they admit that the findings in the paper are only “hypothesis generating,”<sup>121</sup> and I agree. Similarly, the authors do not feature any lung function data among their conclusions. Yet, the authors state elsewhere that “[t]here were no significant changes in [pulmonary function testing] parameters following 12 weeks of treprostinil,” and I note that forced vital capacity was one of the assessed parameters.<sup>122</sup> Indeed, the authors explained that it was “[i]mportant [that] pulmonary function (i.e., degree of

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<sup>117</sup> Saggar 2014 at 00000232.

<sup>118</sup> *Id.* at 00000230-31, abstract.

<sup>119</sup> *Id.* at 00000231-22.

<sup>120</sup> *Id.* at 00000232.

<sup>121</sup> *Id.*

<sup>122</sup> *Id.* at 00000227-28.

PF) remained unaltered during the study and did not likely confound” the reported gas exchange findings. Indeed, in these patients “there were no significant changes in [pulmonary function testing] parameters following 12 weeks of treprostinil.”<sup>123</sup>

145. In conclusion, because Saggar 2014 reports a single-arm<sup>124</sup> chart review, the data Saggar 2014 reports fail to demonstrate that parenteral treprostinil treatment is effective with respect to improved exercise capacity, 6MWD, plasma concentration of NT-proBNP, exacerbations of the interstitial lung disease, clinical worsening events due to the interstitial lung disease, or forced vital capacity (absolute or percent predicted). This is especially the case considering the study in Saggar 2014 was merely a single-center, open-label, uncontrolled, prospective study, and thus subject to the associated limitations and biases as described above—many of which the authors expressly acknowledge. This is also the case because of the reported study’s small sample size and severe selection biases, which as discussed above, very strongly indicate the reported results do not represent PH-ILD patients. Rather the authors conclude that: “These findings are only hypothesis generating and require confirmation in a multicentre, randomised study design.”

### **C. Parikh 2016**

146. Parikh 2016 reports a retrospective, single-center, single-arm, open-label chart review of 80 patients that was conducted to evaluate the safety and tolerability (not efficacy) of high-dose inhaled treprostinil (i.e., > 9 breaths four times daily).<sup>125</sup> Followed patients consisted of all patients diagnosed with WHO Group 1–5 pulmonary hypertension at the Duke University Medical Center PH Clinic that were prescribed high-dose inhaled treprostinil (> 9 breaths four

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<sup>123</sup> *Id.* at 00000228.

<sup>124</sup> *Supra* § VII.

<sup>125</sup> Parikh 2016 at 010599 to -010600.

times daily) prior to August 2012.<sup>126</sup> The authors do not provide criteria for why patients were initiated on inhaled treprostinil, but the authors state that the chart review “only included patients thought to be good candidates for higher dose [inhaled treprostinil].”<sup>127</sup> The chart review was carried out at the Duke University Medical Center PH Clinic, which is a highly specialized tertiary care center.<sup>128</sup> Parikh 2016 reports that nearly two-thirds (and perhaps more) of the followed subjects were also on at least one additional hypertension therapy (number (percentage)):<sup>129</sup>

<b>Concomitant pulmonary hypertension medications</b>	
• Endothelin receptor antagonist	46 (57.5)
• Phosphodiesterase-5 inhibitor	53 (66.3)
• Oxygen (continuous)	46 (57.5)

147. Parikh 2016 further notes that the authors “did not assess the association of high-dose iTRE with the adjustment of other medications such as diuretics.”<sup>130</sup>

148. Parikh 2016 reports that Duke University Medical Center PH Clinic’s “standard [inhaled treprostinil] dosing protocol [was] as follows:”

3 breaths (18 mcg)/initial session, 6 breaths (36 mcg)/second session, and then titration as tolerated, based on side effects, by 1 breath daily until a maximum dosage of 12 breaths (72 mcg) four times daily is achieved (Figure 1). Of note, iTRE initiation (first and second sessions) was performed in clinic under physician supervision with 4 hours in between the sessions.<sup>131</sup>

149. Patient data, if available, was collected at the following three points: 1) baseline: at 9 breaths four times daily inhaled treprostinil up to 3 months prior to beginning inhaled treprostinil; follow-up visit 1: 3–6 months post initiation of high-dose inhaled treprostinil; and 3) follow-up

<sup>126</sup> *Id.*

<sup>127</sup> *Id.* at 010603.

<sup>128</sup> *Id.* at 010600.

<sup>129</sup> *Id.* at 010607, Table 1, 010601.

<sup>130</sup> *Id.* at 010603.

<sup>131</sup> *Id.* at 010600.

visit 2: most recent visit prior to August 2012.<sup>132</sup> Median times from start of high-dose inhaled treprostinil to follow-up visits 1 and 2 were 5.2 months (Q1-Q3: 4.0–8.7) and 20.3 months (Q1-Q3: 14.2–33.2), respectively.<sup>133</sup>

150. Only 78 of the 80 followed patients made it to 12 breaths four times daily, and 20 of those 78 patients discontinued inhaled treprostinil during follow-up.<sup>134</sup> They discontinued for the following reasons:

9 transitioned to parenteral therapy, 4 stopped due to side effects, 3 died, 2 self-discontinued, 1 had worsening [pulmonary hypertension] symptoms on high-dose iTRE (parenteral therapy not appropriate), and 1 had lack of clinical response.<sup>135</sup>

151. Of the 80 followed patients, only 49 patients had data for the follow-up visit 1 analysis and only 39 of those patients continued until follow-up visit 2.<sup>136</sup> If a patient stopped high-dose treprostinil prior to follow-up 1 or follow-up 2 (i.e., if the dose was reduced or if treatment was stopped altogether), data “were collected from the most recent visit closest to the high-dose discontinuation.”<sup>137</sup>

152. Because the chart review reported in Parikh 2016 was an open-label, single-arm chart review, that chart review was by definition neither randomized, blinded, nor placebo-controlled.<sup>138</sup>

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<sup>132</sup> *Id.* at 010601.

<sup>133</sup> *Id.*

<sup>134</sup> *Id.* at 010602.

<sup>135</sup> *Id.*

<sup>136</sup> *Id.* at 010609, Table 2.

<sup>137</sup> *Id.* at 010601.

<sup>138</sup> *Supra* § VII.

**1. Parikh 2016 chart review design imposes significant limitations on findings, some of which were also recognized by the chart reviews authors.**

153. The chart review reported in Parikh 2016 is at least subject to all the limitations associated with single-center studies (particularly those in which the center is highly specialized), uncontrolled nonrandomized single-arm studies, open-label studies, and retrospective studies.<sup>139</sup>

In fact, The authors expressly and correctly caution that:

[Their] study was limited by the retrospective study design and only included patients thought to be good candidates for higher dose iTRE. Because this was an observational study in clinical practice it also suffers from follow-up loss.<sup>140</sup>

154. The authors further and rightly state that “[t]here were insufficient follow-up data to analyze efficacy endpoints.”<sup>141</sup> This makes sense because the primary endpoints of the chart review were safety and tolerability of the treatment, and thus the chart review was not intended to or designed to evaluate the efficacy of inhaled treprostinil in the followed patients.<sup>142</sup> Moreover, all comparisons in Parikh 2016 were made between patients’ baseline and respective follow-up visit data, if available.<sup>143</sup> Such change scores are at least subject to the potential biases outlined above.<sup>144</sup> Importantly, tests of statistical significance in change scores in patients, all of whom received the same treatment—here inhaled treprostinil—cannot be used to draw inferences about the effectiveness of that treatment.<sup>145</sup>

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<sup>139</sup> *Supra* § VII.

<sup>140</sup> Parikh 2016 at 010603.

<sup>141</sup> *Id.*

<sup>142</sup> *Id.* at 010600 (noting that the authors “aimed to characterize safety and tolerability of higher iTRE doses (>9 breaths four times daily and/or greater than 216 mcg/day) from [their] single tertiary center experience in treating PH patients”).

<sup>143</sup> *Id.* at 010600 to 010601.

<sup>144</sup> *Supra* § VII.

<sup>145</sup> *Supra* § VII.

155. The chart review suffers from other shortcomings as well. For example, I cannot be sure about the length of treatment on high-dose inhaled treprostinil that the reported change scores reflect. That is because Parikh 2016 reports that patients' follow-up visits occurred at different times after initiating high-dose inhaled treprostinil (e.g., the time between initiation of high-dose inhaled treprostinil to follow-up visit 1 is reported in one place<sup>146</sup> to range from 3 to 6 months but it is reported elsewhere that the median time to follow-up visit 1 was 5.2 months (about 21 weeks) with the interquartile range being 4.0-8.7 months).<sup>147</sup> The data for follow up visit 2 is worse in this regard, with a median time to follow-up of 20.3 months (approximately 88 weeks) with an interquartile range of 14.2 to 33.2 months. The change scores Parikh 2016 reports therefore reflect a shorter period for some patients and a much longer period for others, but information to even begin to assess this distribution is not reported. The number of patients for which data was available for 16 or fewer weeks on high-dose inhaled treprostinil appears rather low (approximately only 12 subjects).<sup>148</sup> However, Parikh 2016 also reports that follow-up visit 1 data was only available for 49 patients, meaning that about one quarter of patients (25.6%) discontinued inhaled treprostinil during follow-up.<sup>149</sup> The number of patients who discontinued high-dose treprostinil prior to Visit 1 who are reflected in the reported change scores is also not fully or clearly disclosed.<sup>150</sup>

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<sup>146</sup> Parikh 2016 at 010600-600.

<sup>147</sup> *Id.* at 010601.

<sup>148</sup> *Id.* (The lower quartile for Visit 1 times is 4.0 months. The lower quartile is the time at which one-quarter of patients' visits occur. Since only 49 patients had any data available at Follow-up Visit 1, only about a quarter of them, or about 12, had Visit times before 4 months.)

<sup>149</sup> *Id.* at 010609, Table 2.

<sup>150</sup> Parikh 2016 indicates that when a patient discontinued high-dose inhaled treprostinil, that patient's most recent visit relative to the discontinuation would substitute for the follow-up 1 or follow-up 2 visit to which the discontinuation was prior.

156. Likewise, I cannot know what medical condition the reported change scores reflect.

First, Parikh 2016 reports following patients of all WHO Groups 1–5, and of the 80 followed patients, only 6 are reported to have Group 3 interstitial lung disease/fibrosis and only a further 6 are reported to have Group 3 mixed pattern.<sup>151</sup> Second, change scores could only be determined based on data that happened to be present in the patients’ medical record, and as a result, there is substantial loss to follow-up—only 49 of the 80 followed patients had any data available for follow-up visit 1 and it appears that only 39 of those patients continued to follow-up visit 2.<sup>152</sup> Even fewer followed patients had 6MWD and NT-proBNP data available.<sup>153</sup> The reported change scores for these metrics (6MWD and NT-proBNP) were only available for fewer than half of the 80 followed patients: 39 and 34 patients for 6MWD and 32 and 23 patients and for NT-proBNP at follow-up visits 1 and 2, respectively.<sup>154</sup> Parikh 2016 does not report which patients these change scores reflect. Therefore, I cannot tell whether these change scores reflect any of the followed Group 3 interstitial lung disease/fibrosis or Group 3 mixed pattern patients.

**2. Parikh 2016 chart review suffered from severe selection bias and small sample size.**

157. The chart review reported by Parikh 2016 only followed 6 patients reported to have Group 3 interstitial lung disease/fibrosis and only a further 6 patients reported to have Group 3 mixed pattern.<sup>155</sup> With respect to at least these 12 patients, this chart review is at least subject to all the limitations associated with low sample size and selection issues. For example, such a small sample in and of itself indicates that the data reported by Parikh 2016 are unrepresentative of PH-

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<sup>151</sup> *Id.* at 010607, Table 1.

<sup>152</sup> *Id.* at 010609, Table 2.

<sup>153</sup> *Id.* at 010602.

<sup>154</sup> *Id.*

<sup>155</sup> *Id.* at 010607, Table 1.

ILD patients—especially given that these patients were being treated at a highly specialized tertiary center.<sup>156</sup>

158. Moreover, the reported change scores predominantly reflect data obtained from patients who did not have PH-ILD. Only 49/80 patients enrolled had any follow-up data at all, and while the number of PH-ILD patients who had data available for follow-up is not reported, it is likely a small number given that only 15% of patients originally enrolled had PH-ILD.<sup>157</sup> Patients do not drop out at random, and reasons for dropping out are often associated with worsening disease. As noted above, 20 followed subjects discontinued inhaled treprostinil entirely.<sup>158</sup> The authors note that “the most common reason for discontinuing inhaled treprostinil entirely was the need to transition to parenteral therapy for worsening PH.”<sup>159</sup> That was the explanation for 9 followed patients.<sup>160</sup> Parikh 2016 reports that the other 11 followed patients discontinued for the following reasons: “4 stopped due to side effects, 3 died, 2 self-discontinued, . . . and 1 had lack of clinical response.”<sup>161</sup> Systematically removing patients whose disease worsens introduces a severe bias.<sup>162</sup> And while Parikh 2016 explains that a discontinued patient’s most recent visit relative to the discontinuation would substitute for the next follow-up visit,<sup>163</sup> it is unclear how recent the imputed visit was, if it even occurred, and whether it occurred before or after any worsening of symptoms.

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<sup>156</sup> *Id.* at 010600.

<sup>157</sup> *Id.* at 010609, Table 2.

<sup>158</sup> *Id.* at 010602.

<sup>159</sup> *Id.*

<sup>160</sup> *Id.*

<sup>161</sup> *Id.*

<sup>162</sup> *Supra* § VII.

<sup>163</sup> Parikh 2016 at 010601.

**3. Parikh 2016 chart review fails to account for missing data, unclear that any findings reflect PH-ILD subjects.**

159. As noted above, follow-up visit 1 data was unavailable for at least 31 of 80 followed patients, and data were only available for 39 and 34 patients for 6MWD and 32 and 23 patients and for NT-proBNP at follow-up visits 1 and 2, respectively.<sup>164</sup> Due to the extent of the missing data, it is not possible to determine the extent to which data from the 12 followed Group 3 interstitial lung disease/fibrosis and Group 3 mixed pattern patients are reflected in the 6MWD and NT-proBNP change scores reported by Parikh 2016. In fact, because there were only 12 followed Group 3 interstitial lung disease/fibrosis and Group 3 mixed pattern patients and the number of patients with missing data exceeds 12, it is entirely possible that none of the reported change scores, including the 6MWD and NT-proBNP changes scores, reflect data collected from any of these 12 followed patients.

**4. Parikh 2016's cautionary conclusions in view of its limitations.**

160. , In the Conclusion section of the report, the authors of Parikh 2016 draw no conclusions whatsoever concerning the efficacy of inhaled treprostinil for any purpose, either in the overall cohort of patients studied or in any of the WHO subpopulations. I cannot evaluate whether the authors' conclusion that inhaled treprostinil at a dose of >9 breaths four times daily "appears to be safe and generally well-tolerated" is justified by the reported findings, but this conclusion was made in spite of over half of the followed patients being lost to follow-up in some capacity and 20 of the 80 patients discontinuing inhaled treprostinil altogether.<sup>165</sup> Moreover, as noted above, the chart review's limited sample size and substantial selection effects strongly indicate that the reported data are unrepresentative of PH-ILD patients.

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<sup>164</sup> *Id.* at 010602, 010609, Table 2.

<sup>165</sup> *Id.* at 010602 to -010603, -010609, Table 2.

161. The statement that “we report a favorable safety and tolerability profile among PH WHO group 3 patients in our study for whom there are currently no approved therapies, and iTRE may provide benefit in this patient population” is not supported by any sufficient data reported in Parikh 2016. The 6MWD data reported was a small increase of 3.9 meters, but that number is based on a group of patients that includes a population with a mix of WHO group pulmonary hypertension diagnoses, 85 percent of which (68/80) did not have PH-ILD.<sup>166</sup> Moreover, there is good reason to believe the change scores reported by Parikh 2016 do not in fact reflect any WHO Group 3 patients, let alone PH-ILD patients. Not only do I agree with the authors’ statement that “[t]here were insufficient follow-up data to analyze efficacy endpoints[,]”<sup>167</sup> but it is also my opinion there is even less sufficient data to support conclusions concerning PH-ILD patients in Parikh 2016.

162. I disagree with the authors’ statement that “[t]hese results warrant further investigation into the efficacy of high-dose iTRE in PH,” especially regarding PH-ILD patients.<sup>168</sup> The reported change scores show little, if any, clear improvement from baseline, the number of PH-ILD patients who did have 6MWD results was small, and no safety or tolerability data is reported for PH-ILD patients at all.

163. In conclusion, Parikh 2016 is a single-arm chart review, and a single-center, open-label, uncontrolled, retrospective study, with small sample size and selection biases, and is therefore subject to the associated limitations and biases as described above—many of which the authors expressly acknowledge.<sup>169</sup> The data Parikh 2016 reports fail to demonstrate that an inhaled

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<sup>166</sup> *Id.* at - 010603, -010607, Table 1 indicates that only 12 of 80 patients were WHO Group 3 ILD or mixed pattern.

<sup>167</sup> *Id.* at 010603.

<sup>168</sup> *Id.* at 010603.

<sup>169</sup> *Supra* § IX. C. 1-3.

treprostinil treatment is effective with respect to improved exercise capacity, 6MWD, plasma concentration of NT-proBNP, exacerbations of the interstitial lung disease, clinical worsening events due to the interstitial lung disease, or forced vital capacity (absolute or percent predicted). In fact, the authors do not even single out PH-ILD in their conclusions. Rather the authors only conclude that: “These results warrant further investigation into the efficacy of high-dose iTRE in PH.”<sup>170</sup>

**D. Agarwal 2015**

164. Agarwal 2015 is an abstract reporting on a retrospective, single-center, single-arm, open-label chart review following 35 purportedly WHO Group 3 patients that were administered inhaled treprostinil.<sup>171</sup> The 35 followed patients purportedly consisted of 15 presenting with obstructive disease, 15 presenting with restrictive disease, and 5 presenting with mixed obstructive/restrictive.<sup>172</sup> Thus, I understand that the cohort reported on had at least 15 patients who did not have PH-ILD (because I understand that obstructive disease is PH-COPD, a distinct category from PH-ILD).

165. Agarwal 2015 reports that all followed patients had a diagnostic right heart catheter prior to treatment.<sup>173</sup> Agarwal 2015 further reports that the baseline hemodynamics, presumably mean, for the 35 followed patients was “mPAP 44.37 +/- 9.80, PAOP 9.68 +/- 4.71” and “CO 4.7 +/- 1.34, and PVR 8.775WU +/- 4.7625,” although CO and PVR data only reflect 34 of the 35

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<sup>170</sup> Parikh 2016 at 010603.

<sup>171</sup> Agarwal 2015; Mar. 9, 2015 Tyvaso in WHO Group 3 Proof of Concept Review (UTC\_PH-ILD\_082484) (“March 2015 Presentation”) at 082490 (noting that the 35 patients were seen in the Brigham and Women’s Hospital PVD clinic). (“March 2015 Presentation”)

<sup>172</sup> Agarwal 2015. I note that a March 2015 presentation discussing the study published as Agarwal 2015 reflects 10 obstructed patients, 17 restricted, and 8 mixed. March 2015 Presentation at 082492.

<sup>173</sup> Agarwal 2015.

followed patients.<sup>174</sup> Agarwal 2015 reports that all patients started inhaled treprostinil at 3 breaths QID and worked towards a goal of 9 to 12 breaths QID as tolerated.<sup>175</sup>

166. Patients were followed for 6 months (26 weeks), but only 26 of the followed patients remained on inhaled treprostinil for 6 months.<sup>176</sup> Agarwal 2015 reports that discontinuation occurred for the following reasons: “1 death unrelated to therapy, 2 stopped because of intolerance, 3 stopped for lack of efficacy, 2 lost to follow up, and 1 who entered hospice.”<sup>177</sup> Not accounting for these patients reflects a selection bias.<sup>178</sup>

167. The chart review investigated changes in 6MWD, Borg Dyspnea Index (“BDI”), WHO functional class, number of breaths, adverse events, and subjective report of improvement.<sup>179</sup> The chart review 6MWD data only reflects 21 followed patients and also reports changes broken out by obstructive vs. restrictive disease for 6MWD, although the sample sized in each of these groups is not disclosed.<sup>180</sup> The authors report no change in dyspnea or WHO function class over a 6-month period.<sup>181</sup> Agarwal 2015 reports 30 of the 35 followed patients reported “subjective improvement,” but Agarwal 2015 also reports that only 24 of 26 followed patients that continued therapy for 6 months reported improvement.<sup>182</sup> The method by which subjective improvement was measured is not specified nor are the two conflicting reported data points reconciled.

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<sup>174</sup> *Id.*

<sup>175</sup> *Id.*

<sup>176</sup> *Id.*

<sup>177</sup> *Id.*

<sup>178</sup> *Supra* § VII.

<sup>179</sup> Agarwal 2015.

<sup>180</sup> *Id.*

<sup>181</sup> *Id.*

<sup>182</sup> *Id.*

168. Additionally, while not noted in Agarwal 2015, a March 2015 presentation given by Dr. Waxman (“March 2015 Presentation”), one of the authors of Agarwal 2015, indicates that 15 patients received dual therapy for at least a portion of the study, and “tolerated the addition of a systemic pulmonary vasodilator (PDE5i).”<sup>183</sup> It is unclear why this limitation is not acknowledged in Agarwal 2015.

169. Because the chart review reported in Agarwal 2015 was an open-label, single-arm chart review, that chart review was neither randomized, blinded, nor placebo-controlled.<sup>184</sup>

**1. Agarwal 2015 chart review design imposes significant limitations on findings.**

170. Although the authors of Agarwal 2015 neglect to discuss the limitations of the reported chart review, that chart review is at least subject to all the limitations associated with single-center studies, uncontrolled nonrandomized single-arm studies, open-label studies, and retrospective studies.<sup>185</sup> Additionally, Dr. Waxman acknowledged in the March 2015 Presentation that the study was subjected to several limitations, including “[s]mall numbers,” “[h]ighly selected in terms of lung disease,” and “[n]ot a randomized trial.”<sup>186</sup> I agree the study reflects those limitations.

171. In particular, all comparisons Agarwal 2015 reports were made between individual patients’ baselines and respective follow-up data, if available.<sup>187</sup> Such change scores are at least subject to the potential biases outlined above (e.g., § VII above). Importantly, tests of statistical significance in change scores in patients that received the same treatment under study—here inhaled treprostinil—*cannot* be used to draw inferences about the effectiveness of that treatment.

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<sup>183</sup> March 2015 Presentation at 082508.

<sup>184</sup> *Supra* § VII.

<sup>185</sup> *Supra* § VII.

<sup>186</sup> March 2015 Presentation at 082510.

<sup>187</sup> Agarwal 2015

172. Agarwal 2015 provides no indication of how patients were selected for (or excluded from) inclusion in the retrospective review. However, the March 2015 presentation notes that the participants were “newly diagnosed patients ... with severe symptoms” and that the study was “[h]ighly selected in terms of lung disease,” which suggests that the participants likely are not representative of WHO Group 3 PH patients as a whole.<sup>188</sup>

173. Data on 6MWD was available on only 21 of 35 patients—40% of enrolled patients did not have both baseline and 6-month data.<sup>189</sup> This alone reflects a limitation on this study that introduces the possibility of selection bias. While Agarwal 2015 only provides the mean change in 6MWD for all 21 patients—60.85m +/- 92.60<sup>190</sup>—the March 2015 Presentation indicates that the mean change was 44.3m for restricted lung disease patients, 114.6m for obstructive lung disease patients, and 20.3m for mixed lung disease patients.<sup>191</sup> However, the March 2015 Presentation and Agarwal 2015 are inconsistent as to the number of participants with obstructive lung disease, restrictive lung disease, and mixed disease.<sup>192</sup> For example, the March 2015 presentation reflects that 6 mixed patients had 6MWD data, but Agarwal 2015 states that only 5 mixed patients participated in the study.<sup>193</sup> Thus, it is not possible to identify the number of PH-ILD patients included in the 6MWD analysis or the mean change in 6MWD for restricted lung disease patients.

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<sup>188</sup> March 2015 Presentation at 082490, 082510.

<sup>189</sup> Agarwal 2015.

<sup>190</sup> *Id.*

<sup>191</sup> March 2015 Presentation at 082503.

<sup>192</sup> Compare March 2015 Presentation at 082492 (noting 10 obstructive patients, 17 restrictive patients, and 8 mixed patients), with Agarwal 2015 (noting 15 obstructive patients, 15 restrictive patients, and 5 mixed patients).

<sup>193</sup> Compare March 2015 Presentation at -082503 (noting mean change in 6MWD for 6 mixed patients), with Agarwal 2015 (noting 5 mixed patients participating in study).

174. Although Agarwal 2015 reports subjective improvement data and WHO functional class data<sup>194</sup>, these subjective assessments are subject to bias. Bias applies for several reasons, including that clinical settings are fraught with psychological or psychosomatic influences impacting all parties, especially with respect to high-risk poor prognosis patient populations like the PH-ILD population. For example, patients who are receiving a high level of clinical care and attention will often view their disease as improved, even when that may not be supported by objective clinical measurements. Patients who believe that they are on a promising experimental therapy may expect improvement, and that can color their subjective assessment as to whether their condition has improved. Providers can also unintentionally influence these subjective measures as well. That is why assessments of subjective improvement can be highly biased.<sup>195</sup> Multi-center, randomized placebo-controlled studies can mitigate this effect by measuring the extent to which subjective improvement in patients treated with active drug exceed subjective improvement reported by placebo patients and by minimizing the influence any one practitioner or group of practitioners may have.<sup>196</sup>

175. I note that all the comparisons reported in Agarwal 2015 are between 6 month (26 weeks) and baseline data.<sup>197</sup> Agarwal 2015 does not report change scores for 8, 12, or 16 weeks.

**2. Agarwal 2015 chart review suffered from severe selection bias and small sample size.**

176. As noted above, only 21 patients had data on change in 6MWD, an unknown number of which had PH-ILD.<sup>198</sup> Assuming that the PH-CPFE patients count as PH-ILD, we can only conclude that the number of PH-ILD patients for which 6MWD changes are reported is

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<sup>194</sup> Agarwal 2015.

<sup>195</sup> *Supra* § VII.

<sup>196</sup> *Supra* § VII.

<sup>197</sup> Agarwal 2015.

<sup>198</sup> *Id.*; *Supra* ¶ 172.

between 6 and 20, either limit being a very small sample size. Sample sizes for other outcome measures such as WHO functional class and BDI are also not reported in Agarwal 2015, and the sample sizes suggested in the March 2015 presentation for WHO FC and BDI appear to conflict with the overall patient breakdown reported in Agarwal 2015.<sup>199</sup> With respect to any potential sample size for PH-ILD, this chart review is at least subject to all the limitations associated with low sample size. For example, such a small sample in and of itself strongly suggests that the data reported by Agarwal 2015 cannot be representative of PH-ILD patients. This conclusion is bolstered by the March 2015 Presentation, which notes that the participants were “newly diagnosed patients ... with severe symptoms” and that the study was “[h]ighly selected in terms of lung disease,” which indicates that the participants likely are not representative of WHO Group 3 PH patients as a whole.<sup>200</sup>

177. Furthermore, Agarwal 2015 reports that ~26% (9/35) of the followed patients were not included in the outcome assessments because they were on therapy for less than 6 months.<sup>201</sup> The reasons include death (purportedly unrelated to therapy), intolerance of treatment, lack of efficacy, and transfer to hospice.<sup>202</sup> All of these suggest that the followed patients excluded from analysis were systematically sicker than those ultimately included in the reported results. An additional 5 patients did not have 6MWD changes available; the reasons for the missing data are

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<sup>199</sup> Compare March 2015 Presentation at 082500 (noting mean change in WHO FC for 6 mixed patients), and March 2015 Presentation at 082506 (noting mean change in BDI for 6 mixed patients), with Agarwal 2015 (noting 5 mixed patients participating in study).

<sup>200</sup> March 2015 Presentation at 082490, 082510.

<sup>201</sup> Agarwal 2015.

<sup>202</sup> *Id.*

not disclosed,<sup>203</sup> but again this could be because of worsening physical status, which would further bias the reported results.

### 3. Agarwal 2015 conclusions in view of its limitations.

178. In view of the fact that the authors observed no change in dyspnea or functional class in this group of patients, and in view of the fact that changes in 6MWD are not compared to placebo results, I disagree with the authors' efficacy conclusion that "Group-3 PH can be effectively ... treated with iTre [and that i]nhaled Treprostinil *may* offer a well-tolerated treatment in advanced lung disease patients complicated by pulmonary vascular remodeling."<sup>204</sup> I cannot evaluate whether the authors' conclusion regarding safety and tolerance in those same statements is justified. I note that Agarwal 2015 otherwise makes no mention of "pulmonary vascular remodeling," and Agarwal 2015 reports that ~26% (9/35) of the followed patients were not included in the outcome assessments because they discontinued therapy for the reasons listed above.<sup>205</sup> Moreover, as noted above, the chart review's limited sample size suggests that the reported data are unrepresentative of PH-ILD patients in general.

179. In view of all of the limitations on this study, to the extent anyone wished to evaluate, e.g., efficacy of inhaled treprostinil, a more robust trial would be required. Indeed, the authors state that "a prospective clinical trial is indicated."<sup>206</sup> The fact that Agarwal 2015 concludes that such a study is needed shows that the Agarwal 2015 authors believed that their study was insufficient to establish that the method was effective, and that prospective (a placebo-controlled randomized) clinical trial were necessary to do so.

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<sup>203</sup> No explanation is given for the missing data, and the reported statistics do not appear to account for missing data.

<sup>204</sup> Agarwal 2015.

<sup>205</sup> *Id.*

<sup>206</sup> *Id.*

180. In conclusion, because Agarwal 2015 is a single-arm chart review, the data Agarwal 2015 reports fail to demonstrate that an inhaled treprostinil treatment is effective with respect to improved exercise capacity, 6MWD, plasma concentration of NT-proBNP, exacerbations of the interstitial lung disease, clinical worsening events due to the interstitial lung disease, or forced vital capacity (absolute or percent predicted). This is especially the case considering the chart review reported in Agarwal 2015 was merely a single-center, open-label, uncontrolled, retrospective study, and thus subject to the associated limitations and biases as described above. This is also the case because of the reported chart review's small sample size and severe selection biases, which as discussed above, very strongly indicate the reported results do not represent PH-ILD patients. In fact, the authors do not even single out PH-ILD in their conclusions. Rather the authors conclude that: "Group-3 PH can be effectively and safely treated with iTre . . . [and a] prospective clinical trial is indicated."<sup>207</sup>

**E. Faria-Urbina 2018**

181. Faria-Urbina 2018 reports a retrospective, single-site, single-arm, open-label chart review that screened 72 patients presenting with pulmonary hypertension that were administered inhaled treprostinil at the Pulmonary Vascular Disease Clinic at Brigham and Women's Hospital from December 2009 to November 2016.<sup>208</sup> Faria-Urbina 2018 reports that these 72 patients were screened for those patients that had "PH with evidence of pulmonary vascular remodeling" per the following hemodynamic criteria: mPAP  $\geq$  35 mmHg (which the authors' characterize as "severe PH") or a mPAP  $\geq$  25 mmHg associated with pulmonary vascular resistance (PVR)  $\geq$  4 Woods

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<sup>207</sup> *Id.*

<sup>208</sup> Faria-Urbina 2018 at 009936, 009937, abstract.

Units.<sup>209</sup> Patients with isolated postcapillary PH (i.e., high PAWP and normal PVR) were excluded from this cohort.<sup>210</sup>

182. This population was purportedly further screened for lung disease as follows:

Lung disease was defined by as follows: (1) COPD: postbronchodilator FEV1/FVC < 0.7 [19] and/or evidence of emphysema on HRCT; (2) ILD: presence of fibrosis, defined as reticular septal thickening associated with architectural distortion with traction bronchiectasis, or honeycombing on HRCT [20, 21]; (3) CPFE: presence of emphysema and diffuse parenchymal lung disease with significant pulmonary fibrosis on HRCT [22].<sup>211</sup>

183. The remaining 61 subjects were then further screened to exclude the following:

Exclusion criteria included the following: identification of another known cause of PH (such as chronic thromboembolic disease); follow-up < 3 months; treatment with another PH-specific drug added in a period < 3 months from iTre initiation; lung transplantation during follow-up (< 3 months); recent hospitalization due to unstable lung disease (~ 1 month), extemporaneous RHC, and/or inability to review baseline PFT or RHC data.<sup>212</sup>

184. This left 22 purportedly “Group 3 PH” patients for the chart review. Faria-Urbina  
2018 diagrams this screening process as follows:<sup>213</sup>

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<sup>209</sup> *Id.* at 009938, abstract.

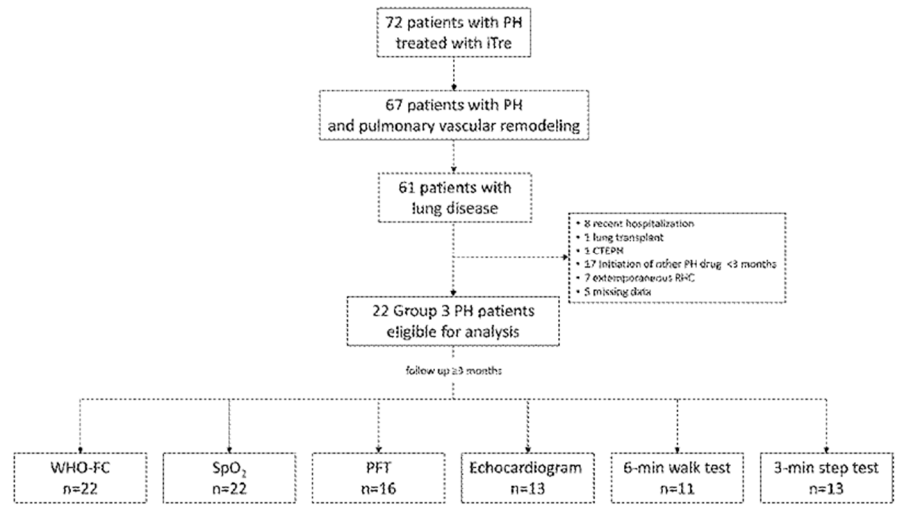
<sup>210</sup> *Id.* at 009938.

<sup>211</sup> *Id.* at 009937.

<sup>212</sup> *Id.*

<sup>213</sup> *Id.* at 009938, Fig. 1.

**Fig. 1** Study flow diagram. *iTre* inhaled treprostinil sodium, *PH* pulmonary hypertension (mPAP  $\geq$  35 mmHg or mPAP  $\geq$  25 mmHg and PVR  $\geq$  3 Woods Units on resting RHC), *CTEPH* chronic thromboembolic pulmonary hypertension, *RHC* right heart catheterization, *WHO-FC* World Health Organization functional class, *SpO<sub>2</sub>* pulse oxygen saturation, *PFT* pulmonary function test, *RHC* right heart catheterization



185. Faria-Urbina 2018 reports that the 22 followed patients consisted of 8 patients presenting with COPD, 9 patients presenting with ILD, and 5 patients presenting with combined disease (CPFE).<sup>214</sup> Faria-Urbina 2018 reports that these patients were administered inhaled treprostinil (“iTRe”) as follows:

All patients consented to receive treatment based on medical judgment [23] after being informed of the potential risks and benefits of iTRe. Patients received iTRe at three breaths (18 µg) four times daily (72 µg/day). iTRe doses were increased as tolerated by three additional breaths (18 µg) per dosing session every 3-7 days to achieve a dose of at least 9-12 breaths or more (~54 µg) four times daily (~216 µg/day) unless limited by side effects. If patients had dose-limiting side effects, then either a slower dose titration or a lower goal dose was prescribed.<sup>215</sup>

186. The authors note that all the followed patients “were on optimized therapies for the treatment of baseline lung disease prior to consideration for iTRe treatment, were followed for at least 3 months, and were compliant with the medication.”<sup>216</sup> The authors also confirmed that the “[t]herapies related to the underlying lung disease were continued throughout the observation

<sup>214</sup> *Id.* at 009938.

<sup>215</sup> *Id.* at 009937.

<sup>216</sup> *Id.*

period.”<sup>217</sup> The chart review followed the 22 patients for at least 3 months.<sup>218</sup> However, follow-up timing and the specific follow-up tests conducted were at the discretion of the treating physician and were not uniform across patients in the study.<sup>219</sup> Notably, at least four of the patients who completed the 6MWD test at baseline and follow-up were treated with dual therapy consisting of treprostinil and either sildenafil or tadalafil during the study.<sup>220</sup> It is unclear whether any other patients also received dual therapy.

187. Because the chart review reported in Faria-Urbina 2018 was an open-label, single-arm chart review, that chart review was by definition neither randomized, blinded, nor placebo-controlled.

**1. Faria-Urbina 2018 chart review design imposes significant limitations on findings.**

188. I note that the authors expressly acknowledge that their chart review is “limited by its retrospective, single-center, observational, uncontrolled design.”<sup>221</sup> I agree. The chart review reported in Faria-Urbina 2018 is subject to all the limitations associated with single-center studies (particularly those where the center is highly specialized), uncontrolled nonrandomized single-arm studies, open-label studies, and retrospective studies discussed in Section VII.<sup>222</sup> For example, Faria-Urbina 2018 only reports differences between patients’ baseline and follow-up visit data.<sup>223</sup> Such change scores are subject to the potential biases outlined above.<sup>224</sup> Importantly, tests of statistical significance in change scores in patients that received the same treatment under study—

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<sup>217</sup> *Id.*

<sup>218</sup> *Id.* at 009937, abstract.

<sup>219</sup> *Id.* at 009937-39, Fig. 1, abstract.

<sup>220</sup> *Id.* at 009940, Fig. 3.

<sup>221</sup> *Id.* at 009941.

<sup>222</sup> *Supra* § VII.

<sup>223</sup> Faria-Urbina 2018 at 009940.

<sup>224</sup> *Supra* § VII

here, inhaled treprostinil—cannot be used to draw inferences about the effectiveness of that treatment.<sup>225</sup>

189. Faria-Urbina 2018 is also subject to limitations associated with studies that have small sample sizes, a heterogenous patient cohort, and an unrepresentative patient cohort (i.e., comprising only patients who meet certain criteria of disease severity).<sup>226</sup> In fact, the authors expressly state that their chart review’s “[r]esults should be interpreted carefully in view of the small sample size and the heterogeneity of the population (COPD, ILD, and CPFE).” I agree. Thus, Dr. Channick’s reliance on the Faria-Urbina 2018 paper is misplaced. There is supplemental data available for Faria-Urbina 2018, and according to that data (which is available separately from the paper itself), the data on change in 6MWD were available on only 11 of 22 followed patients, and the change score reflects a heterogenous population with these 11 followed patients consisting purportedly of 5 patients presenting with COPD, 3 patients presenting with ILD, and 3 patients presenting with CPFE.<sup>227</sup> With respect to the authors’ express concerns regarding heterogeneity, the authors appear to offer the following counterpoint: “a subanalysis of each subgroup (Tables S2-S4) demonstrated the tendency for improved functional class and 6-min walking distance, without significant deleterious effect on SpO2 that was observed in the entire study population was maintained when analyzing each subcohort.”<sup>228</sup> First, I note that the authors acknowledge that

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<sup>225</sup> *Id.*

<sup>226</sup> *Supra* § IX. B

<sup>227</sup> Supplementary Material for Mariana Faria-Urbina et al., *Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease*, 196(2) *Lung* 139 (2018) (“Faria-Urbina 2018 Supplementary Material”) at Tables S2-S4. I note that Faria-Urbina 2018 inconsistently reports the number of followed patients for which follow-up 6MWD data exists. Figure 1, the legend of Figure 3, Table 2, and Tables S2-S4 purport that the data reflects 11 followed patients with 6MWD data, but the text of the “Follow-up assessment” section purports that the data only reflects 10 followed patients.

<sup>228</sup> Faria-Urbina 2018 at 009941.

these subanalyses at most indicate a “tendency” with respect to improved functional class and 6MWD. Second, the authors fail to explain why less skepticism should be directed towards these even smaller sample sizes (e.g., the 6MWD subanalysis change scores reflect 5 followed patients presenting with COPD, 3 followed patients presenting ILD, and 3 followed patients presenting CPFE, respectively) than the authors expressly instruct should be directed to an 22- or 11-patient population.<sup>229</sup> Notably, in view of all these limitations, the authors single out the followed COPD patients—not the followed ILD or CPFE patients—as those who “tended to have greater benefit from iTre treatment by the aforementioned parameters.”<sup>230</sup> Regardless, conclusions about efficacy in terms of 6MWD or otherwise cannot be appropriately drawn about PH-ILD in a sample size of only n=3.

190. Another significant limitation is that some of the patients received other drugs in addition to inhaled treprostinil. For example, of the 11 patients for whom 6MWD data was available, 4 of the patients were also on sildenafil or tadalafil.<sup>231</sup> Each patient was also on an “optimized therap[y] for treatment of baseline lung disease,” which continued throughout the observation period.<sup>232</sup> This limits the ability to discern effects attributable to treprostinil.

191. The authors also note that their findings could be limited by “the intrinsically subjective nature of FC assessment, and the lack of a control group.”<sup>233</sup> I agree as discussed above.<sup>234</sup> The authors note that “All patients [...] were compliant with the medication.” Sackett notes, however, that “[b]ecause high compliance is therefore a marker for better outcomes, even

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<sup>229</sup> Faria-Urbina 2018 Supplementary Material at Tables S2-S4.

<sup>230</sup> Faria-Urbina 2018 at 009941.

<sup>231</sup> *Id.* at 009940, Fig. 3.

<sup>232</sup> *Id.* at 009937.

<sup>233</sup> *Id.* at 009941.

<sup>234</sup> *Supra* § IX.

when treatment is useless, our controlled clinical experiences often will cause us to conclude that compliant patients must have been receiving efficacious therapy.”<sup>235</sup> Assessments of subjective improvement can be highly biased. Multi-center, randomized placebo-controlled studies can mitigate this effect by measuring the extent to which subjective improvement in patients treated with active drug exceed subjective improvement reported by placebo patients and by minimizing the influence any one practitioner or group of practitioners may have.

192. I note that all the comparisons reported in Faria-Urbina 2018 are between at least 3 months (about ~12-13 weeks) and baseline data.<sup>236</sup> Faria-Urbina 2018 does not report change scores for 8 weeks and may not report change scores reflecting 12 weeks or even 16.

**2. Faria-Urbina 2018 chart review suffered from severe selection bias and small sample size.**

193. The chart review reported within the Faria-Urbina 2018 paper only followed 22 patients, of which 9 purportedly presented with ILD and 5 with CPFE.<sup>237</sup> To the extent one looks beyond the reference cited by Dr. Channick to the data supplement, even fewer of these patients had 6MWD data available at follow-up (3 patients purportedly presenting with ILD and 3 patients presenting with CPFE).<sup>238</sup> Whether 9 or 3, either way this chart review is subject to all the limitations associated with low sample size.<sup>239</sup> For example, such small samples in and of themselves indicate that the data reported by Faria-Urbina 2018 are not representative of PH-ILD patients in general.

194. This small patient cohort is also likely to be unrepresentative of PH-ILD patients due to the study’s PVD inclusion criteria (i.e., the hemodynamic requirements), which generally

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<sup>235</sup> Sackett 1989 at 2S.

<sup>236</sup> Faria-Urbina 2018 at 009937 (noting “follow-up  $\leq$  3 months” as exclusion criteria).

<sup>237</sup> *Id.* at 009938.

<sup>238</sup> Faria-Urbina 2018 Supplementary Material at Tables S2-S4.

<sup>239</sup> *Supra* § VII.I.

required severe PH or an indication that pulmonary vascular disease was “the predominant physiopathologic mechanism for PH.”<sup>240</sup> Indeed, the authors expressly acknowledge the “possibl[ity] that [their] results favoring the potential use of iTre in Group 3-PH might have been influenced by the presence of pulmonary vascular disease.”<sup>241</sup> The authors further acknowledge that this selection bias was “by study design.”<sup>242</sup>

195. In addition, the chart review excluded patients with less than 3 months follow-up; those for whom it was necessary to add another PH drug during the follow-up period; those who needed a lung transplantation during follow-up; and those with recent hospitalization due to unstable lung disease.<sup>243</sup> These exclusions eliminated 27 patients who would be expected to have worse functional outcomes than the 22 patients studied who did not meet those criteria. This introduces an optimistic bias into any assessment of efficacy.

### **3. Faria-Urbina 2018 chart review fails to account for missing data.**

196. Although the chart review followed 22 patients, only half of them had 6MWD data available in their records after the follow-up period.<sup>244</sup> The reasons for half of the study sample missing follow-up 6MWD data are not disclosed. The statistical methods do not account for missing data, and no clear explanation is offered in the article. The article suggests that whether to perform the 6MWD assessment was based on the treating physicians’ judgments for each patient.<sup>245</sup> A physician’s judgment that a patient’s condition was too severe to safely and successfully perform or complete the 6MWD test could be one reason for not performing the test;

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<sup>240</sup> Faria-Urbina 2018 at 009938.

<sup>241</sup> *Id.* at 009941.

<sup>242</sup> *Id.*

<sup>243</sup> *Id.* at 009937.

<sup>244</sup> *Id.* at 009940, Fig. 3.

<sup>245</sup> *Id.* at 009937.

such a reason would tend to remove patients who could not or would not perform well from the set of patients analyzed, thereby introducing this bias along with others into the reported 6MWD change scores.

**4. Faria-Urbina 2018 conclusions in view of its limitations.**

197. The conclusion section of Faria-Urbina 2018 begins with the authors again acknowledging that the reported chart review was retrospective.<sup>246</sup> The authors then conclude that the chart review demonstrated that inhaled treprostinil sodium (iTre) was safe in patients with Group 3 PH and evidence of pulmonary vascular remodeling.<sup>247</sup> The authors similarly conclude that “iTre was well tolerated, with no serious adverse events reported.”<sup>248</sup> However, these conclusions are apparently based on the 22 non-excluded patients, and must therefore assume that none of the reasons for exclusion (such as 17 patients who required additional PH drugs, or 8 who developed unstable lung disease) could possibly be attributed to inhaled treprostinil. Moreover, these conclusions are necessarily limited to the patient population to which the chart review was directed: a highly screened sample cohort arrived at by applying inclusion criteria indicating severe PH and/or pulmonary vascular remodeling and exclusion criteria that appear to have excluded higher risk patients.<sup>249</sup> Moreover, as noted above, the chart review’s limited sample size indicates that the reported data are unlikely to be representative of PH-ILD patients.<sup>250</sup>

198. The authors also conclude that “iTre improved WHO-FC and 6MWT distance, without deleterious effects on resting SpO<sub>2</sub>.”<sup>251</sup> This conclusion, however, runs contrary to the

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<sup>246</sup> *Id.* at 009941.

<sup>247</sup> *Id.* at 009941, abstract.

<sup>248</sup> *Id.*

<sup>249</sup> *Id.* at 009937.

<sup>250</sup> *Supra* § VII.I.

<sup>251</sup> Faria-Urbina 2018 at 009938.

limitations the authors expressly raised and that I discuss, above.<sup>252</sup> Moreover, as discussed above, tests of statistical significance in change scores in patients that receive the same treatment under study—here, inhaled treprostinil—*cannot* be used to draw inferences about the effectiveness of that treatment.

199. The authors also conclude that “the potential role of inhaled PH-specific drugs in Group 3 PH should be further assessed in large prospective studies.”<sup>253</sup> I am not convinced that the data in this retrospective chart review actually do suggest a further study was warranted, but it is true that a larger, prospective, well-controlled, randomized, and blinded study would be necessary to arrive at conclusions regarding efficacy concerning such measures as o6MWD. A more robust study would be required to inquire into “the potential role of inhaled PH-specific drugs in Group 3 PH,” in view of the significant limitations of the present study. In my opinion, the authors do not go far enough in merely recommending “large prospective studies,” as they overlook the need to blind and randomize their proposed next study and to expand it to multiple centers. The authors further conclude that, absent their “large prospective studies,” inhaled treprostinil’s “use in Group 3 PH should be cautiously evaluated in specialized PH Centers, after an individualized assessment and risk-benefit consideration.”<sup>254</sup> Assuming this recommendation reflects the standard of care for these patients when this data was reported, I agree that the reported data do not demonstrate a treatment effect that would justify any deviation from this standard of care, especially absent significant further testing, for example, in a multi-center, double-blinded, randomized, placebo-controlled trial.

200. Notably, the authors do not single out PH-ILD in their conclusions.

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<sup>252</sup> *Id.* at 009941.

<sup>253</sup> *Id.*

<sup>254</sup> *Id.*

201. In conclusion, because Faria-Urbina 2018 is a single-arm chart review, the data that Faria-Urbina 2018 reports fail to demonstrate an inhaled treprostinil treatment effect with respect to improved exercise capacity, 6MWD, plasma concentration of NT-proBNP, exacerbations of the interstitial lung disease, clinical worsening events due to the interstitial lung disease, or forced vital capacity (absolute or percent predicted). This is especially the case considering the chart review reported in Faria-Urbina 2018 was merely a single-arm, single-center, open-label, uncontrolled, retrospective chart review, and thus subject to the associated limitations and biases as described above—many of which the author’s expressly acknowledge. This is also the case because of the reported chart review’s small sample size and severe selection biases, which as discussed above very strongly indicate the reported results do not represent PH-ILD patients. In fact, the authors do not even single out PH-ILD in their conclusions. Rather the authors conclude that “[t]he potential role of inhaled PH-specific drugs in Group 3 PH should be further assessed in larger prospective studies. Until then, its use in Group 3 PH should be cautiously evaluated in specialized PH Centers, after an individualized assessment and risk-benefit consideration.”

## **X. THE INCREASE AND PERFECT STUDIES**

202. The INCREASE and PERFECT studies were multi-center, randomized, double-blind, placebo-controlled studies of inhaled treprostinil vs. placebo in patients with PH-ILD and PH-COPD, respectively.

### **A. The INCREASE Study**

203. The INCREASE trial was a multi-center, randomized, double-blind, placebo-controlled study of inhaled treprostinil vs. placebo in patients with PH-ILD.<sup>255</sup> The study enrolled 326 patients, half of whom were randomized to receive inhaled treprostinil and half to receive

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<sup>255</sup> Waxman 2021.

placebo inhalation.<sup>256</sup> The primary endpoint was change in peak 6MWD from baseline to week 16; secondary endpoints included change in plasma NT-proBNP, time to clinical worsening, and changes in peak and trough 6MWD from baseline to weeks 12 and 15, respectively.<sup>257</sup> Endpoints were specified, and protocols for measuring them were detailed in advance in a detailed study protocol document.<sup>258</sup> Statistical methods were also pre-defined in a statistical analysis plan and were posted to ClinicalTrials.gov in advance of carrying out the study.<sup>259</sup> The statistical analysis plan included methods for taking account of the effects of any missing data.<sup>260</sup>

### **1. The 2017 INCREASE Study Description**

204. The INCREASE trial, entitled “A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects With Pulmonary Hypertension Due to Parenchymal Lung Disease,” was pre-registered with ClinicalTrials.gov prior to conducting the trial and was assigned study number NCT02630316.<sup>261</sup> Version 23 was posted to ClinicalTrials.gov on February 10, 2017.<sup>262</sup> That update describes the proposed study to be carried out, including the basic elements of study design, the interventions to be studied, the outcome measures, and patient eligibility.<sup>263</sup> Version 24, which was posted on March 3, 2017, updated and clarified the study description, secondary outcomes measures, and

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<sup>256</sup> *Id.*

<sup>257</sup> *Id.* at 010809.

<sup>258</sup> United Therapeutics Corp., RIN-PH-201 Statistical Analysis Plan for “A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease” (Feb. 27, 2019) (UTC\_PH-ILD\_057509) (“INCREASE Stat. Analysis Plan”) at 057514 - 057515.

<sup>259</sup> *Id.* at 057514 - 057515.

<sup>260</sup> *Id.* at 057514 - 057515.

<sup>261</sup> Version 1 of ClinicalTrials.gov Posting for “Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE” (NCT02630316) (Dec. 15, 2015) (“NCT02630316 Version 1”).

<sup>262</sup> Version 23 of ClinicalTrials.gov Posting for “Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE” (NCT02630316) (Feb. 10, 2017) (LIQ\_PH-ILD\_00000185) (“2017 INCREASE Study Description”).

<sup>263</sup> *Id.*

participant eligibility criteria.<sup>264</sup> Version 85, which was posted on January 10, 2020, updated the study recruitment status from “recruiting” to “completed.”<sup>265</sup> Version 88, which was posted on June 6, 2020, updated the secondary outcome measures to add “Time to Clinical Worsening.”<sup>266</sup> Study results were first submitted to ClinicalTrials.gov on April 29, 2021, and were first posted on May 24, 2021.<sup>267</sup> At no time prior to April 17, 2020—indeed, at no time prior to May 24, 2021—were any INCREASE study results or findings reported on ClinicalTrials.gov.

## **2. The INCREASE Study Publication**

205. The results of the study were published in the *New England Journal of Medicine* on January 13, 2021.<sup>268</sup> Dr. Aaron Waxman was the principal author and Steven D. Nathan was the senior author of the paper. Many elements of the study, including disclosure of its design, methods, execution, analysis, and results are also disclosed in the Examples of U.S. Provisional Patent Application No. 63/011,810, U.S. Provisional Patent Application No. 63/160,611, and the ’327 patent.

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<sup>264</sup> Version 24 of ClinicalTrials.gov Posting for “Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE” (NCT02630316) (Mar. 3, 2017) (“NCT02630316 Version 24”) (limiting secondary outcome measures to “Change in Peak 6-minute Walk Distance (6MWD) from Baseline to Week 12,” “Change in Trough 6-minute Walk Distance (6MWD) from Baseline to Week 15,” and “Change in plasma concentration of N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) from Baseline to Week 16.”).

<sup>265</sup> Version 85 of ClinicalTrials.gov Posting for “Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE” (NCT02630316) (Jan. 10, 2020) (“NCT02630316 Version 85”).

<sup>266</sup> Version 88 of ClinicalTrials.gov Posting for “Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE” (NCT02630316) (June 2, 2020) (“NCT02630316 Version 88”).

<sup>267</sup> Version 89 of ClinicalTrials.gov Posting for “Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE” (NCT02630316) (May 24, 2021) (“NCT02630316 Version 89”).

<sup>268</sup> Waxman 2021 at 010790.

### 3. The PERFECT Study

206. The PERFECT study was a multi-center, randomized, double-blind, placebo-controlled, 12-week crossover trial of inhaled treprostinil to treat PH-COPD.<sup>269</sup> The results were published in the *European Respiratory Journal* in April 2024.<sup>270</sup> The principal author was Steven D. Nathan and the senior author was Aaron Waxman. The study was pre-registered on ClinicalTrials.gov (NCT03496623) in April 2018, entitled, “A Phase 3, Randomized, Placebo-controlled, Double-blind, Adaptive Study to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Patients With Pulmonary Hypertension Due to Chronic Obstructive Pulmonary Disease (PH-COPD).”<sup>271</sup> The primary endpoint was change from baseline in 6MWD after 12 weeks of active treatment compared to change from baseline in 6MWD after placebo treatment.<sup>272</sup>

207. The study was terminated before its planned completion after the Data and Safety Monitoring Committee (DSMC) determined that patients on the active treatment (inhaled treprostinil) experienced serious adverse events at a greater rate compared to patients receiving placebo treatment.<sup>273</sup> These serious adverse events included those leading to hospitalization.<sup>274</sup> Five deaths occurred while on treprostinil and no deaths occurred while on placebo. The DSMC also “noted that the changes in 6MWD ... were numerically worse with iTRE exposure than with placebo exposure ... .”<sup>275</sup>

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<sup>269</sup> Steven D. Nathan et al., *Inhaled Treprostinil in Pulmonary Hypertension Associated With COPD: PERFECT Study Results*, 63 Eur. Respiratory J. (2024) (“Nathan 2024”) at 2-3.

<sup>270</sup> *Id.*

<sup>271</sup> Version 1 of ClinicalTrials.gov Posting for “A Phase 3 Adaptive Study to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Participants With Pulmonary Hypertension (PH) Due to Chronic Obstructive Pulmonary Disease (COPD) (PERFECT)” (NCT03496623) (Apr. 12, 2018) (“NCT03496623 Version 1”).

<sup>272</sup> Nathan 2024 at 5.

<sup>273</sup> *Id.* at 5, Table 3.

<sup>274</sup> *Id.* at 5.

<sup>275</sup> *Id.*

208. The authors concluded that “the results of this study indicated that patients receiving iTRE experienced numerically more events for AEs, SAEs, deaths, treatment discontinuations and study discontinuations compared with placebo. In addition, patients treated with iTRE showed no improvement in 6MWD when compared with placebo. Overall, this study showed that the risks in treating PH-COPD patients with iTRE outweighed the potential positive benefits, thereby justifying its early termination.”<sup>276</sup>

209. The authors identified several limitations to the study having to do with the pace of study recruitment and the effects of the COVID-19 epidemic in obtaining study measurements. Nonetheless, the study failed to show efficacy or safety in PH-COPD patients.

**B. The Results Of INCREASE and PERFECT Demonstrate Why Dr. Channick’s Cited References Do Not Reliably Predict Inhaled Treprostinil’s Therapeutic Benefit in PH-ILD and PH-COPD Patients**

210. Agarwal 2015’s retrospective study reports numerical average changes from baseline in 6MWD in the selected patients studied, such as patients with restrictive, obstructive, or mixed restrictive/obstructive WHO Group 3 pulmonary hypertension.<sup>277</sup> Similarly, Faria-Urbina 2018’s retrospective study also reports numerical changes from baseline in 6MWD in PH patients with COPD, ILD, and CPFE.<sup>278</sup> Dr. Channick has rendered the opinion that a POSA as of the priority date would have interpreted these results to mean that inhaled treprostinil is safe and would improve 6MWD in Group 3 PH patients, without regard to the obstructive or restrictive character of the disease.<sup>279</sup> I disagree with Dr. Channick’s analysis.

211. The prospective, randomized, double-blind, multi-center INCREASE and PERFECT studies reached differing conclusions. The INCREASE study demonstrated that

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<sup>276</sup> *Id.* at 10.

<sup>277</sup> Agarwal 2015.

<sup>278</sup> Faria-Urbina 2018.

<sup>279</sup> Channick Op. Rept. at ¶¶ 119-127, ¶¶ 217-221.

inhaled treprostinil was safe and effective in improving 6MWD in PH-ILD patients receiving placebo.<sup>280</sup> By contrast, the PERFECT study demonstrated that administering inhaled treprostinil to PH-ILD patients with PH-COPD was not safe and showed no evidence of efficacy in improving 6MWD as compared to patients receiving placebo.<sup>281</sup> These opposite conclusions for inhaled treprostinil treatment of PH-ILD (restrictive WHO Group 3) and PH-COPD (obstructive WHO Group 3) patients illustrate why the studies Dr. Channick and Liquidia rely on do not stand for the principles claimed in this litigation. Liquidia and Dr. Channick cite small, single-arm, retrospective studies such as Agarwal 2015 and Faria-Urbina 2018 and assert that the data in them demonstrates improved exercise capacity, 6MWD, and other measures. I disagree for the reasons above but if we assume for the sake of argument that the data points in that direction, it would also equally point in that direction for PH-COPD (if not more strongly). The opposite results of INCREASE and PERFECT show why the conclusions in small, limited, pilot studies with all of the limitations above do not support the conclusions Liquidia and Dr. Channick read into them. The POSA would understand that results of studies, particularly chart reviews evaluating patients with restrictive and/or obstructive WHO Group 3 PH in single-arm retrospective studies cannot reliably predict outcomes from well-conducted, definitive randomized controlled clinical trials.

## **XI. DR. CHANNICK'S REPORT**

212. Dr. Channick's report relies on the references above and I therefore disagree with his opinions for the reasons I have explained above regarding the limitations and biases in the studies and patent he cites. Here I will further address Dr. Channick's Opening Expert Report and offer opinions on matters of statistics and study design related to his opinions.

### **A. The INCREASE Study is not merely studying more patients than Agarwal**

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<sup>280</sup> *Supra* § X.

<sup>281</sup> *Supra* § X.

**2015 and Faria-Urbina 2018.**

213. Dr. Channick asserts that the INCREASE study is merely a retelling of the chart reviews reported in Agarwal 2015 and Faria-Urbina 2018 but with a larger number of patients, and thus, greater power to obtain a significant result.<sup>282</sup> For example, Dr. Channick asserts:

Statistical significance is a matter of adequately powering a study with a sufficient number patients. In fact, the '327 patent did nothing more than evaluate the same drug, administered by the same route of administration, using the same dosing as Faria-Urbina 2018 and, as Dr. Waxman admitted, in the same PH-ILD population. The '327 patent simply studied more PH-ILD patients than Faria-Urbina 2018, but reached the identical conclusion.<sup>283</sup>

Dr. Channick further asserts:

To the extent UTC contends that the results are unexpected because a statistically significant result was achieved, I disagree. The '327 patent simply studies more PH-ILD patients than Agarwal 2015 and Faria-Urbina 2018, but used the identical route of administration and identical dosing.<sup>284</sup>

Dr. Channick is wrong, for multiple reasons.

214. First, Dr Channick's is wrong that "[s]tatistical significance is a matter of adequately powering a study with a sufficient number patients." As noted above, statistical power (and hence the likelihood of obtaining a statistically significant result) depends on much more than just sample size.<sup>285</sup> Crucially, statistical power depends upon the specific question that the statistical test is designed to answer.<sup>286</sup> Here, Faria-Urbina 2018 and Agarwal 2015 report chart reviews posing questions that their significance tests address that are entirely different from the ones that the INCREASE study posed.<sup>287</sup> The significance tests in the two single-arm chart reviews

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<sup>282</sup> Channick Op. Rept. at ¶¶ 303-306, 403, and 423.

<sup>283</sup> Channick Op. Rept. at ¶ 303.

<sup>284</sup> Channick Op. Rept. at ¶ 403; *id* at ¶ 423 ("As I explained above, treating PH-ILD with inhaled treprostinil was well known in the art long before April 17, 2020, and the '327 patent merely studied inhaled treprostinil in a larger patient population").

<sup>285</sup> *Supra* § VII.

<sup>286</sup> *Supra* § VII.

<sup>287</sup> *Supra* § VII; *compare supra* § IX.D, and § IX.E, with § X.A.

address the question as to whether the particular patients in those studies saw a change, e.g., in 6MWD, on average over time (6 months and 3 months for Agarwal 2015 and Faria-Urbina 2018, respectively).<sup>288</sup> The significance tests reported in the INCREASE study address the question as to whether a certain effect (such as change in 6MWD) was greater in patients receiving inhaled treprostinil as opposed to patients who did not receive treprostinil but who were otherwise treated in the same manner, that is, was inhaled treprostinil effective.<sup>289</sup> Thus, while p-values and the notion of statistical significance were used in both the chart reviews and in the INCREASE study, they were addressing to completely different questions. Achieving statistical significance in the former context is completely unrelated to and uninformative about achieving statistical significance in the latter. Because no patients who did *not* receive treprostinil were included in the retrospective studies cited by Dr. Channick, those studies could not possibly answer the question addressed in the INCREASE study, no matter how large the sample size.<sup>290</sup> Dr. Channick's position is based on hindsight, not statistical principles.

215. Dr. Channick also asserts:

Given that statistical significance is a matter of mathematical power, and Dr. Waxman was seeing benefits in treating PH-ILD patients with inhaled treprostinil, a statistically significant change in any metric is obvious in light of the prior art.<sup>291</sup>

This position is also erroneous and a reflection of hindsight, not statistical principles.<sup>292</sup> As noted above, statistical significance is not simply a matter of mathematical power.<sup>293</sup> Moreover, the purported “benefits” Dr. Waxman reported in Faria-Urbina 2018 and purportedly observed in his

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<sup>288</sup> *Supra* §§ VII, IX.D, IX.E.

<sup>289</sup> *Supra* §§ VII, X.A.

<sup>290</sup> *Supra* § VII; compare *supra* § IX.D, and § IX.E, with § X.A.

<sup>291</sup> Channick Op. Rept. at ¶ 304.

<sup>292</sup> *Supra* § VII.

<sup>293</sup> *Supra* § VII.

patients may or may not have been a consequence of that treatment as discussed above.<sup>294</sup> As described above, the measurements for 6MWD reported in Faria-Urbina 2018 were only compared to each individual patients' baseline 6MWD. Because the 6MWD data reported in Faria-Urbina 2018 were not subjected to, e.g., a comparison between treprostinil-treated patients' change from baseline in 6MWD *and* placebo-treated patients' change from baseline in 6MWD, there is no way to know if the purportedly observed treatment effect was due to treprostinil, to or chance, or to some other cause. By Dr. Channick's reasoning, the purported "benefits" that Agarwal 2015 and Faria-Urbina 2018 report in PH-COPD patients would similarly imply a significant positive change in any metric—something we know from the PERFECT study is not the case.<sup>295</sup>

216. Moreover, anecdotal data collected in a non-systematic manner with no control over what data are included and with no scope for comparison to a standard are less reliable than the retrospective single-arm studies discussed above.<sup>296</sup> Combining such data and performing statistical calculations cannot produce results of higher quality or reliability than the underlying data on which they are based.<sup>297</sup> Yet reliance on anecdote is precisely the flawed position that Dr. Channick advances.<sup>298</sup> In other words, Dr. Channick's unsupported assertion that it is "clear that if a statistical analysis were conducted on all the patients being treated, there would be statistically significant improvements in 6MWD and other metrics" is incorrect.<sup>299</sup> For the reasons I have identified in this report, the POSA would not interpret Dr. Channick's cited references as sufficiently showing, e.g., that inhaled treprostinil improves exercise capacity.

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<sup>294</sup> Channick Op. Rept. at ¶ 304; *supra* §§ VII, IX.E.

<sup>295</sup> *Supra* §§ VII, IX.D, IX.E, X.

<sup>296</sup> *Supra* § VII.

<sup>297</sup> *Supra* § VII.

<sup>298</sup> Channick Op. Rept. at ¶¶ 304-305 (citing alleged use by physicians "since 2009").

<sup>299</sup> Channick Op. Rept. at ¶ 305.

217. Dr. Channick's report frequently cites to materials, e.g., depositions from this litigation, in its treatment of this subject matter.<sup>300</sup> Because these materials would not have been available to the POSA these materials do not support Dr. Channick's positions.

**B. Dr. Channick mischaracterizes or ignores the deficiencies of Saggar 2014, Parikh 2016, Agarwal 2015, and Faria-Urbina 2018.**

218. Dr. Channick mischaracterizes aspects of Saggar 2014, Parikh 2016, Agarwal 2015, and Faria-Urbina 2018. I discuss these issues below.

**1. Saggar 2014**

219. Dr. Channick fails to acknowledge that that Saggar 2014 merely reports a single-arm study.<sup>301</sup> However, because Saggar 2014 merely reports a single-arm study, that means that Saggar 2014 only reports change scores when reporting comparisons—i.e., differences between patients' baseline and follow-up visits.<sup>302</sup> Tests of statistical significance in change scores in patients that received the same treatment under study—here, parenteral treprostinil—*cannot* be used to draw inferences about the effectiveness of that treatment.<sup>303</sup> This applies to the 6MWD, FVC, BNP, BDI, UCSD SOB, and SF-36 change scores that Dr. Channick's Report references.<sup>304</sup> For example, Dr. Channick's Report states that:

Patients showed 'significant improvements in right heart haemodynamics' as well as '6MWD improvements following 12 weeks of parenteral treprostinil therapy (mean 59 m; p<0.001)',<sup>305</sup>

220. Dr. Channick and his report failed to account for the limitations of a single-arm study—like that reported in Saggar 2014—and the change scores they produce.<sup>306</sup> These are not

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<sup>300</sup> Channick Op. Rept. ¶¶ 248, 263-264.

<sup>301</sup> *Supra* §§ VII, IX.B; Saggar 2014 at 123-24; Channick Op. Rept. at ¶¶ 30, 114-18, 308-16.

<sup>302</sup> *Supra* §§ VII, IX.B; Saggar 2014 at 123-29.

<sup>303</sup> *Supra* §§ VII, IX.B.

<sup>304</sup> *Supra* § VII; Channick Op. Rept. at ¶¶ 30, 117, 309-310, 312-313.

<sup>305</sup> Channick Op. Rept. at ¶ at 309.

<sup>306</sup> *Supra* §§ VII, IX.B; Saggar 2014 at 123-24; Channick Op. Rept. at ¶¶ 30, 114-18, 308-16.

equivalent to demonstrating that treprostinil has a treatment effect with respect to any of these metrics.<sup>307</sup> In fact, the authors of Saggar 2014 expressly acknowledge “[t]he absence of a placebo arm [as] a particularly significant limitation.”<sup>308</sup> Critically, Dr. Channick’s report ignores this.<sup>309</sup>

221. As discussed above, because Saggar 2014 is a single-arm study, the data Saggar 2014 reports fail to demonstrate an inhaled treprostinil treatment effect with respect to improved exercise capacity, 6MWD, plasma concentration of NT-proBNP, exacerbations of the interstitial lung disease, clinical worsening events due to the interstitial lung disease, or forced vital capacity (absolute or percent predicted).<sup>310</sup> This is especially the case considering the study reported in Saggar 2014 was merely a single-arm, single-center, open-label, uncontrolled, prospective, and thus subject to the associated limitations and biases as described above—many of which the author’s expressly acknowledge.<sup>311</sup> This is also the case because of the reported study’s small sample size and severe selection biases, which as discussed above strongly indicate the reported results do not represent PH-ILD patients.<sup>312</sup>

222. Dr. Channick does, however, acknowledge that the authors of Saggar 2014 concluded that their findings “require confirmation in a multicentre, randomised study design.”<sup>313</sup> The POSA would understand that that is the authors’ acknowledging of the limitations of their study—that the data generated could not demonstrate a parental treprostinil treatment effect and could at most produce “hypothesis generating” data.<sup>314</sup> In my opinion this is consistent with the

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<sup>307</sup> *Supra* §§ VII, IX.B.

<sup>308</sup> Saggar 2014 at 128.

<sup>309</sup> Channick Op. Rept. at ¶¶ 30, 114-18, 308-16.

<sup>310</sup> *Supra* §§ VII, IX.B; Saggar 2014 at 123-29.

<sup>311</sup> *Supra* §§ VII, IX.B; Saggar 2014 at 123-29.

<sup>312</sup> *Supra* §§ VII, IX.B; Saggar 2014 at 123-25.

<sup>313</sup> Channick Op. Rept. at ¶ 314.

<sup>314</sup> *Supra* §§ VII, IX.B; Saggar 2014 at 128-29.

express limitations that Saggar 2014 report.<sup>315</sup> In particular, the authors' expressly state "[a]t this point, the routine use of PH-targeted therapy in PF-PH is not recommended and should only be cautiously considered at specialized PH centres to avoid the serious potential for worsening cardiopulmonary status in this patient population."<sup>316</sup> Dr. Channick's report does not address this.<sup>317</sup> Yet this statement is a further recognition that there was still significant unknowns and concerns and that the data Saggar 2014 reported was not convincing.<sup>318</sup>

223. Dr. Channick further neglects potential bias impacting the reported data. For example, the reported study was open label and many of the assessments were subjective, e.g., BDI, UCSD SOB, and SF-36.<sup>319</sup> As noted above, these subjective assessments are typically highly sensitive to bias unless performed in a multi-center, randomized, double-blinded, placebo-controlled study.<sup>320</sup> Also, as discussed above, the reported study reflects a limited sample size (15 subjects) that is likely unrepresentative of PH-ILD patients.<sup>321</sup> This may be due to selection bias arising from the study site.<sup>322</sup>

224. In reference to the percent predicted FVC results that Saggar 2014 reports, Dr. Channick asserts that:

This 1% change is comparable to the 1.1% change described in the INCREASE Study whose results were published in 2021 in the New England Journal of Medicine article titled Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease ("NEJM Publication") which reports it as a significant improvement in FVC. Thus, to the extent the INCREASE Study and the '327 patent

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<sup>315</sup> *Supra* §§ VII, IX.B; Saggar 2014 at 128.

<sup>316</sup> *Supra* § IX.B; Saggar 2014 at 128.

<sup>317</sup> Channick Op. Rept. at ¶¶ 30, 114-18, 308-16.

<sup>318</sup> *Supra* § IX.B; Saggar 2014 at 123-26.

<sup>319</sup> *Supra* § VII, IX.B; Saggar 2014 at 128.

<sup>320</sup> *Supra* § VII, IX.B.

<sup>321</sup> *Supra* § VII, IX.B; Saggar 2014 at 123-29.

<sup>322</sup> *Supra* § VII, IX.B; Saggar 2014 at 123-29.

report that a 1.1% effect is significant, so too is the improvement reported in Saggar 2014.<sup>323</sup>

Dr. Channick makes a number of errors, including a pretty fundamental statistical error. First, Dr. Channick is clearly incorrect when he argues that the Saggar 2014 FVC findings are statistically significant even though Saggar 2014 clearly reports that the observed 1% increase over individual patient baselines was *not* statistically significant—Table 2 reports a p-value of 0.687, which is far from the benchmark for statistical significance of 0.05.<sup>324</sup> In fact, Saggar 2014 states that “[t]here were *no significant changes* in PFT parameters following 12 weeks of treprostinil.”<sup>325</sup> Second, simply because a difference of a particular magnitude was found to be a statistically significant difference in one study has no bearing whatsoever on whether the same magnitude of difference would be statistically significant in another study.

225. Moreover, Dr. Channick mischaracterizes the results of the INCREASE study.<sup>326</sup> The “1.1% effect” to which Dr. Channick refers is the average increase over individual baseline in the treprostinil group of patients at 16 weeks.<sup>327</sup> But this is *not* what the statistical analysis (and statistical significance) reported in INCREASE refers to.<sup>328</sup> The calculation of statistical significance is based on the difference between the change seen in the treprostinil group (+1.07%) and the corresponding change seen in the placebo group (-0.72%).<sup>329</sup> This difference of 1.80% is what the INCREASE study reports to be statistically significant ( $p=0.03$ ).<sup>330</sup> Thus, even if his

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<sup>323</sup> Channick Op. Rept. at ¶ 332; *id.* at ¶ 117.

<sup>324</sup> *Compare* Channick Op. Rept. at ¶¶ 117, 332, with Saggar 2014 at 125; *supra* § IX.B.

<sup>325</sup> Saggar 2014 at 125; *supra* § IX.B.

<sup>326</sup> Channick Op. Rept. at ¶¶ 117, 332.

<sup>327</sup> *Compare* Channick Op. Rept. at ¶¶ 117, 332, with Waxman 2021 at 010825.

<sup>328</sup> Waxman 2021 at 010825.

<sup>329</sup> Waxman 2021 at 010825; *supra* § VII.

<sup>330</sup> Waxman 2021 at 010792 - 010793, 010825; *supra* § VII.

assertions about statistical significance in one setting automatically carries over to another setting—which it does not—he would still have equated apples to oranges.

226. Dr. Channick further asserts that a POSA would have been motivated to combine the “improvements in FVC” reported in Saggar 2014.<sup>331</sup> I disagree. As would the Saggar 2014 publication that expressly stated “[t]here were *no significant changes* in PFT parameters following 12 weeks of treprostinil.”<sup>332</sup> Saggar 2014 also states “[i]mportantly, pulmonary function (i.e., degree of PF) remained unaltered during the study and did not likely confound these findings.”<sup>333</sup> Interestingly, Dr. Channick quotes presumably recent deposition testimony of the principal author of Saggar 2014, Dr. Rajan Saggar, who—according to Dr. Channick—now asserts Saggar 2014 “shows that 10 out of the 15 patients had significant improvements in their FVCs.”<sup>334</sup> There are several problematic issues to note here. First, either Dr. Channick or Dr. Saggar appears to be using the term “significant” to mean “clinically important,” which is a concept completely unrelated to statistical significance.<sup>335</sup> Second, seeing 10 of 15 patients show increases while 5 of 15 show decreases in FVC is consistent with increasing being equally likely as decreasing, that is, could easily be due to chance. Third, the clinical observation that some patients saw an improvement and others saw decline when treated using the same regimen is hardly supportive of a treatment effect.<sup>336</sup>

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<sup>331</sup> Channick Op. Rept. at ¶¶ 30, 114-18, 308-16..

<sup>332</sup> *Supra* § IX.B; Saggar 2014 at 125.

<sup>333</sup> *Supra* § IX.B; Saggar 2014 at 127.

<sup>334</sup> Channick Op. Rept. at ¶ 311; Saggar 2014 at 123 (listing Dr. Rajan Saggar as the principal author of Saggar 2014).

<sup>335</sup> *Compare supra* § VII, with Channick Op. Rept. at ¶ 311.

<sup>336</sup> *Supra* § VII.

227. Dr. Channick's report frequently cites to materials, e.g., depositions from this litigation, in its treatment of Saggar 2014.<sup>337</sup> Because these materials would not have been available to the POSA these materials do not support Dr. Channick's positions.

## 2. Parikh 2016

228. Dr. Channick fails to acknowledge that Parikh 2016 merely reports a single-arm chart review.<sup>338</sup> However, because Parikh 2016 merely reports a single-arm chart review, that means that Parikh 2016 only reports change scores when reporting comparisons—i.e., differences between patients' baseline and follow-up visits.<sup>339</sup> Tests of statistical significance in change scores in patients that received the same treatment under study—here, inhaled treprostinil—*cannot* be used to draw inferences about the effectiveness of that treatment.<sup>340</sup> This applies to the 6MWD and NT-proBNP change scores that Dr. Channick's Report references:

The study found that the average increase in the 6-minute walk distance was 3.9 meters from Baseline to Followup Visit 1, and 31.6 meters from Baseline to Follow-up Visit 2.443 Additionally, NT-proBNP decreased by 39 ng/L at Follow-up Visit 1 and 630 ng/L at Follow-up 2.<sup>341</sup>

Dr. Channick and his report failed to account for the limitations of a single-arm chart review—like that reported in Parikh 2016—and the change scores they produce.<sup>342</sup> These are not equivalent to demonstrating that treprostinil has a treatment effect with respect to any of these metrics such as through a robust randomized and controlled clinical trial.<sup>343</sup>

229. Dr. Channick also asserts “the successful results disclosed in Parikh 2016 provide a POSA with a reasonable expectation of successfully treating PH-ILD with inhaled

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<sup>337</sup> See, e.g., Channick Op. Rept. ¶¶ 311, 314-316.

<sup>338</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 1-5; Channick Op. Rept. at ¶¶ 34, 256-259.

<sup>339</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 1-5.

<sup>340</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 1-5.

<sup>341</sup> Channick Op. Rept. at ¶¶ 34, 256-259.

<sup>342</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 1-5; Channick Op. Rept. at ¶¶ 34, 256-259.

<sup>343</sup> *Supra* §§ VII, IX.C.

treprostinil.”<sup>344</sup> I disagree. Parikh 2016 does not disclose any successful efficacy results.<sup>345</sup> None of the change of the 6MWD or NT-proBNP change scores achieved statistical significance, i.e., these change scores were not statistically significantly different from zero.<sup>346</sup> Moreover, Parikh 2016, expressly states that “[t]here were insufficient follow-up data to analyze efficacy endpoints.”<sup>347</sup>

230. Additionally, Dr. Channick mischaracterizes the results that Parikh 2016 reported. First, Parikh 2016 did not find (or report) that PH-ILD patients showed an improvement in the 6MWD.<sup>348</sup> Instead, patients diagnosed with PH-ILD were probably among the collection of the patients with PH of a wide variety of etiologies (WHO Groups 1–5) for whom, in aggregate, increased 6MWD was observed.<sup>349</sup> Parikh 2016 reports no findings related specifically to PH-ILD patients.<sup>350</sup> I say “probably” here because of the 80 followed patients only 6 patients were reported to have Group 3 interstitial lung disease/fibrosis and only a further 6 patients were reported to have Group 3 mixed pattern.<sup>351</sup> However, less than half of the original patients were evaluated for changes in 6MWD at follow-up visit 1, so it is unknown how many of 6 Group 3 interstitial lung disease/fibrosis patients and 6 Group 3 mixed pattern patients, if any, are reflected in the results reported by Parikh 2016.<sup>352</sup>

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<sup>344</sup> *Supra* §§ VII, IX.C; Channick Op. Rept. at ¶ 259.

<sup>345</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 1-5.

<sup>346</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 4.

<sup>347</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 5.

<sup>348</sup> *Supra* §§ VII, IX.C; *compare* Channick Op. Rept. at ¶¶ 34, 256-259, *with* Parikh 2016 at 1-5.

<sup>349</sup> *Supra* § IX.C; Parikh 2016 at 1-5.

<sup>350</sup> *Supra* § IX.C; Parikh 2016 at 1-5.

<sup>351</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 9.

<sup>352</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 1-5, 8-12.

231. Second, Dr. Channick's Report omits key caveats regarding the data that were available for the chart review reported in Parikh 2016.<sup>353</sup> Critically, it is impossible to tell when patients' follow up visits occurred as discussed above.<sup>354</sup> That is because follow-up visits were permitted to have occurred with a wide range of time intervals.<sup>355</sup> Parikh reports that the median times from start of high-dose inhaled treprostinil to follow-up visits 1 and 2 were 5.2 months (Q1-Q3: 4.0–8.7) and 20.3 months (Q1-Q3: 14.2–33.2), respectively.<sup>356</sup> As explained above these numbers raise questions as to whether any of the reported data reflect Group 3 interstitial lung disease/fibrosis patients and Group 3 measured sooner than 16 weeks after initiation of inhaled treprostinil.<sup>357</sup>

232. Dr. Channick also asserts that Parikh 2016 concludes that "Group-3 PH can be effectively and safely treated with iTre [and that i]nhaled Treprostinil *may* offer a well-tolerated treatment in advanced lung disease patients complicated by pulmonary vascular remodeling."<sup>358</sup> As discussed above, I disagree with these conclusions to the extent they pertain to efficacy.<sup>359</sup> As mentioned above, Parikh 2016 reported a single-arm chart review.<sup>360</sup> Because Parikh 2016 is a single-arm chart review, the data Parikh 2016 reports fail to demonstrate an inhaled treprostinil treatment effect with respect to improved exercise capacity, 6MWD, plasma concentration of NT-proBNP, exacerbations of the interstitial lung disease, clinical worsening events due to the

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<sup>353</sup> *Supra* §§ VII, IX.C; compare Channick Op. Rept. at ¶¶ 34, 256-259, with Parikh 2016 at 1-5, 8-12.

<sup>354</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 2-3.

<sup>355</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 2-3.

<sup>356</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 3.

<sup>357</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 2-3.

<sup>358</sup> Channick Op. Rept. at ¶ 258.

<sup>359</sup> *Supra* §§ VII, IX.C.

<sup>360</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 1-5.

interstitial lung disease, or forced vital capacity (absolute or percent predicted).<sup>361</sup> This is especially the case considering that the chart review reported in Parikh 2016 was merely a single-center, open-label, uncontrolled, retrospective chart review, and thus subject to the associated limitations and biases as described above.<sup>362</sup> This is also the case because of the reported chart review's small sample size and severe selection biases, which as discussed above strongly indicate the reported results do not represent PH-ILD patients.<sup>363</sup>

233. Dr. Channick also mischaracterizes Parikh 2016's findings in terms of PH-ILD patients:

In 2016, researchers from Duke University, in a UTC funded study reviewed 6MWD data from WHO Group 1–5 patients treated with inhaled treprostinil and reported an improvement in the 6MWD in the retrospective study, including in patients with PH-ILD.<sup>364</sup>

Dr. Channick also states that Parikh 2016 reported that the average increase in 6MWD was 3.9 meters at Follow-up Visit 1 and 31.6 m at Follow-up Visit 2.<sup>365</sup> There are several problems with these statements. First, this is only based on the 39 and 34 patients who had follow-up Visits 1 and 2, respectively.<sup>366</sup> Indeed, Parikh 2016 notes “follow-up loss” as a limitation of the reported chart review.<sup>367</sup> Moreover, Parikh 2016 reports that the “the most common reason for discontinuation was the need to transition to parenteral therapy for worsening PH.”<sup>368</sup> It therefore follows that those who dropped out due to poor results—e.g., need for more aggressive therapy, death—were

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<sup>361</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 1-5.

<sup>362</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 1-5.

<sup>363</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 1-5.

<sup>364</sup> Channick Op. Rept. at ¶ 34.

<sup>365</sup> *Id.* at ¶ 258.

<sup>366</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 3-4.

<sup>367</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 5.

<sup>368</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 4.

removed or treated differently for study purposes.<sup>369</sup> This artificially increased the average increase in 6MWD among those who were left.<sup>370</sup>

234. I also disagree with Dr. Channick's statement that "the successful results disclosed in Parikh 2016 provide a POSA with a reasonable expectation of successfully treating PH-ILD with inhaled treprostinil."<sup>371</sup> The "successful results" refer to observations of a heterogeneous cohort of PH patients.<sup>372</sup> The report provides no separate results for PH-ILD patients, which in any case could only be based on at most 6 patients.<sup>373</sup> The report provides no indication as to whether the results seen in the broad population making up the bulk of the data on which the results are based is at all consistent with the results in the subset of patients with ILD.<sup>374</sup> Consequently, it is hard to see how such a paper would be at all informative about the likelihood of successfully treating PH-ILD with inhaled treprostinil.

235. Dr. Channick's report frequently cites to materials, e.g., depositions from this litigation, in its treatment of Parikh 2016.<sup>375</sup> Because these materials would not have been available to the POSA these materials do not support Dr. Channick's positions.

### 3. Agarwal 2015

236. Dr. Channick asserts that "Agarwal 2015 discloses patients who were prospectively treated with inhaled treprostinil but retrospectively analyzed."<sup>376</sup> I disagree with that characterization as detailed above.<sup>377</sup> Agarwal 2015 does not describe anything about

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<sup>369</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 2-4.

<sup>370</sup> *Supra* §§ VII, IX.C.

<sup>371</sup> Channick Op. Rept. at ¶ 259.

<sup>372</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 1-5, 9.

<sup>373</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 1-5, 9.

<sup>374</sup> *Supra* §§ VII, IX.C; Parikh 2016 at 1-12.

<sup>375</sup> *See, e.g.*, Channick Op. Rept. ¶¶ 257, 259, 282.

<sup>376</sup> Channick Op. Rept. at ¶ 219.

<sup>377</sup> *Supra* §§ VII, IX.D.

“prospectively treat[ing]” patients with inhaled treprostinil.<sup>378</sup> However, as detailed above, Agarwal 2015 does report a retrospective, single-center, single-arm, open-label chart review.<sup>379</sup> Because Agarwal 2015 merely reports a single-arm chart review, Agarwal 2015 only reports change scores when reporting comparisons—i.e., differences between patients’ baseline and follow-up visit.<sup>380</sup> Tests of statistical significance in change scores in patients that received the same treatment under study—here, inhaled treprostinil—*cannot* be used to draw inferences about the effectiveness of that treatment.<sup>381</sup> This applies to the 6MWD change scores that Dr. Channick’s Report references, e.g., “Agarwal 2015 further reports that the mean change in 6MWD as ‘+60.85m +/- 92.60 (median change +45m, p = 0.0019),’ which demonstrated a statistically significant improvement.”<sup>382</sup> Dr. Channick and his report failed to account for the limitations of a single-arm chart review—like that reported in Agarwal 2015—and the change scores they produce.<sup>383</sup> These are not equivalent to demonstrating that treprostinil has a treatment effect with respect to any of these metrics.<sup>384</sup>

237. Dr. Channick notes that Agarwal 2015 concludes that “Group-3 PH can be effectively and safely treated with iTre [and that i]nhaled Treprostinil *may* offer a well-tolerated treatment in advanced lung disease patients complicated by pulmonary vascular remodeling.”<sup>385</sup>

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<sup>378</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>379</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>380</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>381</sup> *Supra* §§ VII.

<sup>382</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828; Channick Op. Rept. at ¶¶ 188, 221, 371; *id.* at ¶¶ 221, 371 (cites the change score that Agarwal 2015 reports for the restrictive patients that were followed and have 6 month 6MWD data available: an improvement 50m ± 57 (median +61m). I note that the change score did not even achieve statistical significance. Agarwal 2015 at 009828.

<sup>383</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828; Channick Op. Rept. at ¶¶ 188, 221, 371.

<sup>384</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>385</sup> Channick Op. Rept. at ¶¶ 33, 188, 221.

As discussed above, I disagree with these conclusions to the extent they pertain to efficacy.<sup>386</sup> This is at least because Agarwal 2015 reported a single-arm chart review.<sup>387</sup> Because Agarwal 2015 is a single-arm chart review, the data Agarwal 2015 reports fail to demonstrate an inhaled treprostinil treatment effect with respect to improved exercise capacity, 6MWD, plasma concentration of NT-proBNP, exacerbations of the interstitial lung disease, clinical worsening events due to the interstitial lung disease, or forced vital capacity (absolute or percent predicted).<sup>388</sup> This is especially the case considering that the chart review reported in Agarwal 2015 was merely a single-center, open-label, uncontrolled, retrospective study, and thus subject to the associated limitations and biases as described above.<sup>389</sup> This is also the case because of the reported chart review's small sample size and severe selection biases, which as discussed above, strongly indicate the reported results do not represent PH-ILD patients.<sup>390</sup>

238. Indeed, as Dr. Channick's report notes, the authors of Agarwal 2015 conclude that "[a] prospective clinical trial is indicated."<sup>391</sup> As noted above, I in part agree with that assessment in that Agarwal 2015 has failed to demonstrate that inhaled treprostinil has a treatment effect in Group 3 PH patients and demonstrating this would require further clinical study.<sup>392</sup> The fact that Agarwal 2015 asserts that such a study is needed shows that the Agarwal 2015 authors believed that their study was insufficient to establish that the method was effective, and that a placebo-controlled randomized study was necessary to do so.<sup>393</sup> I also, believe the authors' conclusions

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<sup>386</sup> *Supra* §§ VII, IX.D.

<sup>387</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>388</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>389</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>390</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>391</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828; Channick Op. Rept. at ¶ 221.

<sup>392</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>393</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

concern a trial in Group 3 PH, not a trial focused on PH-ILD.<sup>394</sup> That is consistent with the focus of Agarwal 2015,<sup>395</sup> although Dr. Channick's report appears to ignore that fact.<sup>396</sup>

239. As for the authors' conclusions regarding safety and tolerability this is discussed above.<sup>397</sup> I cannot evaluate whether those statements of clinical opinion are justified. Yet I again note that Agarwal 2015 reports that ~26% (9/35) of the followed patients were not included in the outcome assessments because they discontinued therapy for the reasons detailed above.<sup>398</sup> The discontinued patients appear not to have figured in the safety of tolerability assessments. Those patients that were excluded appear to have been systematically sicker than those ultimately included in the reported results, suggesting the reported change scores are too optimistic.

240. Dr. Channick's report also begins to reveal how exceedingly few patients are reflected by the change scores reported by Agarwal 2015.<sup>399</sup> As noted above, only 21 patients had data on change in 6MWD, an unknown number of whom had PH-ILD.<sup>400</sup> Sample sizes for other outcome measures such as WHO functional class and BDI were not reported.<sup>401</sup> With respect to any potential sample size for PH-ILD, this chart review is at least subject to all the limitations associated with low sample size.<sup>402</sup> As noted above, such a small sample in and of itself strongly indicates that the data reported by Agarwal 2015 are not representative of PH-ILD patients.<sup>403</sup>

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<sup>394</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>395</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>396</sup> Channick Op. Rept. at ¶¶ 33, 185-188, 217-221.

<sup>397</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>398</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>399</sup> Channick Op. Rept. at ¶¶ 186, 219; *supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>400</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>401</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>402</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>403</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

241. Dr. Channick's report is otherwise silent with respect to the limitations of the chart review reported in Agarwal 2015 merely being a single-center, open-label, uncontrolled, retrospective study that are discussed above.<sup>404</sup> Each of these limitations is associated with biases that further prevent any conclusion that Agarwal 2015 demonstrates an inhaled treprostinil treatment effect in Group 3 PH patients let alone PH-ILD.<sup>405</sup> For example, Dr. Channick's report references that Agarwal 2015 reported that 24 of the 26 patients who remained on inhaled treprostinil for 6 months reported subjective improvement.<sup>406</sup> As discussed above, these subjective assessments are typically highly sensitive to bias, especially in unblinded studies.<sup>407</sup>

242. Additionally, while not noted in Agarwal 2015, the March 2015 Presentation given by Dr. Waxman, one of the authors of Agarwal 2015, indicates that 15 patients received dual therapy for at least a portion of the study, and "tolerated the addition of a systemic pulmonary vasodilator (PDE5i)."<sup>408</sup> It is unclear why this limitation is not acknowledged in Agarwal 2015.<sup>409</sup> Dr. Channick's report does not address this.<sup>410</sup>

243. Dr. Channick's report frequently cites to materials, e.g., depositions from this litigation, in its treatment of Agarwal 2015.<sup>411</sup> Because these materials would not have been available to the POSA these materials do not support Dr. Channick's positions.

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<sup>404</sup> Channick Op. Rept. at ¶¶ 33, 185-188, 217-221; *supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>405</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>406</sup> Channick Op. Rept. at ¶¶ 188, 221; *supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>407</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>408</sup> March 2015 Presentation at 082508; Agarwal 2015 at 009828 (listing Dr. Waxman as an Agarwal 2015 author).

<sup>409</sup> *Supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>410</sup> Channick Op. Rept. at ¶¶ 33, 185-188, 217-221; *supra* §§ VII, IX.D; Agarwal 2015 at 009828.

<sup>411</sup> Channick Op. Rept. ¶¶ 37, 186-187, 366.

#### 4. Faria-Urbina 2018

244. Dr. Channick fails to acknowledge that that Faria-Urbina 2018 merely reports a single-arm (“uncontrolled”) chart review, and thus Faria-Urbina 2018 only reports change scores—differences between patients’ respective baselines and follow-up visits.<sup>412</sup> Tests of statistical significance in change scores in patients that received the same treatment under study (inhaled treprostinil in this chart review) *cannot* be used to draw inferences about the effectiveness of that treatment.<sup>413</sup> This applies to the WHO functional class, SpO2, and 6MWD change scores that Dr. Channick’s Report references.<sup>414</sup> Although Dr. Channick’s Report references the Faria-Urbina 2018 authors’ statements that “therapy with iTre significantly improved WHO-FC and 6MWT distance, with no significant changes in resting SpO2 and supplemental oxygen therapy requirement during follow-up”; that the reported “results suggest that iTre is . . . evidence of pulmonary vascular remodeling in terms of functional class, gas exchange, and exercise capacity”; and that Faria-Urbina 2018 saw significant improvements in the 6MWD,<sup>415</sup> Dr. Channick fails to account for the limitations of a single-arm chart review—like those reported in Faria-Urbina 2018—and the change scores the author reports produce.<sup>416</sup> Those change scores are not equivalent to demonstrating that treprostinil has a treatment effect with respect to any of these metrics.<sup>417</sup> Indeed the Faria-Urbina 2018 authors flag that their chart review is “uncontrolled” and “the lack of a control group,”<sup>418</sup> and they state this first among their chart review’s limitations.<sup>419</sup> Critically, Dr. Channick’s report ignores this.

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<sup>412</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009936 to 009941.

<sup>413</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009936 to 009941.

<sup>414</sup> *Supra* §§ VII, IX.E; Channick Op. Rept. at ¶¶ 35, 123.

<sup>415</sup> Channick Op Rept. at ¶¶ 35, 123; Faria-Urbina 2018 at 009936, 009939.

<sup>416</sup> *Supra* §§ VII, IX.E.

<sup>417</sup> *Supra* §§ VII, IX.E.

<sup>418</sup> Faria-Urbina 2018 at 009941.

<sup>419</sup> Faria-Urbina 2018 at 009941.

245. As discussed above, because Faria-Urbina 2018 is a single-arm chart review, the data Faria-Urbina 2018 reports fail to demonstrate an inhaled treprostinil treatment effect with respect to improved exercise capacity, 6MWD, plasma concentration of NT-proBNP, exacerbations of the interstitial lung disease, clinical worsening events due to the interstitial lung disease, or forced vital capacity (absolute or percent predicted).<sup>420</sup> This is especially the case considering the chart review reported in Faria-Urbina 2018 was merely a single-arm, single-center, open-label, uncontrolled, retrospective chart review, and thus subject to the associated limitations and biases as described above—many of which the author’s expressly acknowledge.<sup>421</sup> This is also the case because of the reported chart review’s small sample size and severe selection biases, which as discussed above strongly indicate the reported results do not represent PH-ILD patients.<sup>422</sup>

246. Indeed, as discussed above, the Faria-Urbina 2018 authors not only identify their chart review’s “uncontrolled” nature as a limitation they also state that their chart review was “limited by its retrospective, single-center, observational . . . design.”<sup>423</sup> I also note that the chart review is unblinded and non-randomized.<sup>424</sup> Therefore, as discussed above, this chart review is at least subject to all the limitations associated with single-center studies, uncontrolled nonrandomized single-arm studies, open-label studies, and retrospective studies.<sup>425</sup> Again, limitations that Dr. Channick’s report critically ignores.

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<sup>420</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009936 to 009941.

<sup>421</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009936 to 009941.

<sup>422</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009936 to 009938.

<sup>423</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009941.

<sup>424</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009936 to 009938.

<sup>425</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009936 to 009938.

247. Dr. Channick's report also has to reveal how exceedingly few patients are reflected by the change scores reported by Faria-Urbina 2018.<sup>426</sup> For example, the 6MWD change score at most reflects 11 patients, only 6 of whom have PH-ILD.<sup>427</sup> Again, as noted above, the authors expressly instruct that their "[r]esults should be interpreted carefully in view of the small sample size and the heterogeneity of the population (COPD, ILD, and CPFE)."<sup>428</sup> Accordingly, this chart review is at least subject to all the limitations associated with low sample size, especially with respect to any potential sample size for PH-ILD.<sup>429</sup> For example, such a small sample and the selection effects that led to it in and of themselves strongly indicates that the data reported by Faria-Urbina 2018 are not representative of Waxman PH-ILD patients.<sup>430</sup> Dr. Channick's report omits this.

248. Moreover, Dr. Channick's report asserts that Faria-Urbina 2018 reported improvements in WHO functional class,<sup>431</sup> but Dr. Channick neglects to address that the authors of Faria-Urbina 2018 also note that their findings could be limited by "the intrinsically subjective nature of FC assessment, and the lack of a control group."<sup>432</sup> The authors' recognition of yet another limitation of their chart review is appropriate.<sup>433</sup> Yet Faria-Urbina 2018 also reports that whether to perform the 6MWD assessment was based on the treating physicians' judgments for each patient. A physician's judgment that a patient lacked the exercise capacity to successfully

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<sup>426</sup> *Supra* §§ VII, IX.E; Channick Op. Rept. at ¶¶ 121, 123; Faria-Urbina 2018 at 009936 to 009941; Faria-Urbina 2018 Supplementary Material.

<sup>427</sup> *Supra* § IX.E; Faria-Urbina 2018 at 009938 to 009940; Faria-Urbina 2018 Supplementary Material.

<sup>428</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009941.

<sup>429</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009936 to 009941.

<sup>430</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009936 to 009941; Faria-Urbina 2018 Supplementary Material.

<sup>431</sup> Channick Op. Rept. at ¶ 123.

<sup>432</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009941.

<sup>433</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009941.

complete the 6MWD test could be one reason for not performing the test; such a reason would tend to remove patients who would not perform well from the set of patients analyzed, thereby introducing at least this bias into the reported 6MWD change scores.

249. As discussed above, assessments of subjective improvement can be highly biased, especially in single-center chart reviews like Faria-Urbina 2018.<sup>434</sup> Dr. Channick's report makes it clear that Dr. Waxman was a strong advocate of his hypotheses.<sup>435</sup> For example, Dr. Channick's report remarks on Dr. Waxman's reasoning for conducting the chart review reported in Faria-Urbina 2018, which appears to only have been based on biological plausibility and reasoning by analogy:

During his presentation, Dr. Waxman stated that 'treatment directed at pulmonary remodeling should potentially benefit any patient with a form of pulmonary vascular disease' and that 'pathways that are active in patients with PAH are also active in patients with Group 3 and even Group 2 and Group 3 and even Group 5 [patients].'<sup>436</sup>

Dr. Channick's report purports that it was this belief that led to Dr. Waxman "prospectively" treating patients.<sup>437</sup> If true, this information is consistent with the severe selection bias evident in Faria-Urbina 2018 that I discuss above.<sup>438</sup> The authors even expressly recognized such bias, cautioning that the "possibl[ity] that [their] results favoring the potential use of iTRe in Group 3-PH might have been influenced by the presence of pulmonary vascular disease."<sup>439</sup> The authors further acknowledge that this selection bias was "by study design."<sup>440</sup> Dr. Channick's report does not address this.

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<sup>434</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009937.

<sup>435</sup> Channick Op. Rept. at ¶120.

<sup>436</sup> Channick Op. Rept. at ¶120.

<sup>437</sup> Channick Op. Rept. at ¶120.

<sup>438</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009936 to 009938.

<sup>439</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009941.

<sup>440</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009941.

250. Moreover, as discussed above, the initial screening that the authors applied to arrive at the 22 followed patients excluded over twenty patients based on criteria that excluded patients with less than 3 months follow-up; those for whom it was necessary to add another PH drug during the follow-up period; those who needed a lung transplantation during follow-up; and those with recent hospitalization due to unstable lung disease.<sup>441</sup> These exclusions eliminated at least 27 patients who would be expected to have worse functional outcomes than the 22 followed patients who did not meet those criteria.<sup>442</sup> As noted, this introduces an optimistic bias into the results Faria-Urbina 2018 reports.<sup>443</sup> Dr. Channick's report ignores this as well.

251. Multi-center, randomized, placebo-controlled studies are necessary to mitigate this effect by measuring the extent to which subjective improvement in patients treated with active drug exceed subjective improvement reported by placebo patients and by minimizing the influence any one practitioner—like Dr. Waxman (—or group of practitioners—like Dr. Waxman's)—may have.<sup>444</sup>

252. Critically, as noted above, the authors expressly instruct that “the potential role of inhaled PH-specific drugs in Group 3 PH should be further assessed in larger prospective studies.”<sup>445</sup> Since the purpose of such prospective clinical trials is to determine whether, and if to what extent, inhaled treprostinil was an effective method for improving exercise capacity, it is clear that the authors, including Dr. Waxman, felt that there was insufficient information to draw such a conclusion absent the prospective clinical trials.<sup>446</sup> It is not surprising that Dr. Channick

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<sup>441</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009938.

<sup>442</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009938.

<sup>443</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009938.

<sup>444</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009936 to 009938.

<sup>445</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009941.

<sup>446</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009941.

overlooks these critical details, in view of the misguided misunderstanding of clinical trial study design and statistical principles that are reflected in his report and that I addressed above.<sup>447</sup>

253. Moreover, Dr. Channick ignores that the authors of Faria-Urbina 2018 are almost exclusively focused on Group 3 PH, not PH-ILD.<sup>448</sup> The authors report that “a subanalysis of each subgroup (Tables S2-S4) demonstrated the *tendency* for improved functional class and 6-min walking distance, without significant deleterious effect on SpO2 that was observed in the entire study population was maintained when analyzing each subcohort.”<sup>449</sup> As I note above, this demonstrates that the authors acknowledged that these subanalyses at most indicate a “tendency” with respect to improved functional class and 6MWD.<sup>450</sup> In view of these subanalyses, the authors also only single out the followed COPD patients for note—not the ILD or CPFE patients—stating that these COPD patients “tended to have greater benefit from iTre treatment by the aforementioned parameters.”<sup>451</sup>

254. Dr. Channick’s report also raises the transcripts of two Dr. Waxman presentations. One was Dr. Waxman’s presentation in 2017 at the 12th Annual John Vane Memorial Symposium and the other occurred in 2018 at UTC’s Science Day.<sup>452</sup> Dr. Channick’s report indicates that on both occasions Dr. Waxman was presenting the data reported in Faria-Urbina 2018.<sup>453</sup> Accordingly, all the limitations and biases discussed in this section and above that apply to the

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<sup>447</sup> *Supra* § VII, XI.A; Channick Op. Rept. at ¶¶ 303-306, 403, and 423.

<sup>448</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009936, 009941.

<sup>449</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009941(emphasis added); Faria-Urbina 2018 Supplementary Material.

<sup>450</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009941.

<sup>451</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009941.

<sup>452</sup> Channick Op. Rept. at ¶¶ 120 (John Vane Memorial Symposium), 124 (John Vane Memorial Symposium), 125 (UTC Science Day).

<sup>453</sup> Channick Op. Rept. at ¶¶ 120 (John Vane Memorial Symposium), 124 (John Vane Memorial Symposium), 125 (UTC Science Day).

data reported by Faria-Urbina 2018 necessarily would apply to the data Dr. Waxman presented.<sup>454</sup>

Moreover, portions of each presentation that Dr. Channick's report cite are consistent with Dr.

Waxman understanding the limited nature of the chart review reported by Faria-Urbina 2018.<sup>455</sup>

For example, at the 12th Annual John Vane Memorial Symposium, Dr. Waxman states:

And so to finish up, hopefully, you'll agree that at least these pilot findings do provide some support -- additional support that the treatment of precapillary pulmonary arterial hypertension in patients with advanced lung disease ought to be considered. And that these findings also provide additional evidence supporting more at -- larger clinical trials in patients with this form of pulmonary vascular disease.<sup>456</sup>

This clearly is a limited statement, and Dr. Waxman merely views the chart review data reported

in Faria-Urbina 2018 as supporting "more" or "larger" clinical trials.<sup>457</sup> But a POSA would

understand Dr. Waxman's use of the term "clinical trial" to refer to a prospective randomized

controlled study,<sup>458</sup> which would be necessary to identify a treprostinil treatment effect with

respect to improved exercise capacity.<sup>459</sup> By so recommending, it appears to me that he is

acknowledging that his group's chart review reflects an extremely low number of subjects, that it

only reflects a single center, and that it cannot be relied on to make an assessment of efficacy.<sup>460</sup>

255. At UTC's Science Day, Dr. Waxman stated:

So we felt that this pilot study, again, retrospective, gave us preliminary evidence that there was good reason to consider treating patients with pre-capillary pulmonary hypertension in the setting of advanced lung disease, and this led to

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<sup>454</sup> *Supra* §§ VII, IX.E; Channick Op. Rept. at ¶¶ 120 (John Vane Memorial Symposium), 124 (John Vane Memorial Symposium), 125 (UTC Science Day).

<sup>455</sup> *Supra* §§ VII, IX.E.

<sup>456</sup> Transcript of 12th Annual John Vane Memorial Symposium, March 17, 2017 (LIQ\_PH-ILD\_00147328) ("2017 Waxman Tr.") at -00147344.

<sup>457</sup> *Id.*

<sup>458</sup> *Id.*

<sup>459</sup> *Supra* §§ VII, IX.E.

<sup>460</sup> *Supra* §§ VII, IX.E.

discussions with United Therapeutics and development of 2 clinical trials, the INCREASE study and the PERFECT study.<sup>461</sup>

Dr. Waxman clearly acknowledges that Faria-Urbina 2018 merely reported a retrospective chart review.<sup>462</sup> Dr. Waxman also states that it only provided “preliminary evidence that there was good reason to consider treating patients with pre-capillary pulmonary hypertension in the setting of advanced lung disease.”<sup>463</sup> Dr. Waxman’s statement suggests that Faria-Urbina 2018 was not immediately persuasive to United Therapeutics, who as the statement indicates needed to develop not one but two clinical trials—the INCREASE study directed to PH-ILD and the PERFECT study directed to PH-COPD.<sup>464</sup> As discussed above, Faria-Urbina 2018 expressly emphasizes that PH-COPD patients tended to have greater benefit from inhaled treprostinil.<sup>465</sup> Yet it is the PERFECT study of PH-COPD patients that failed.<sup>466</sup>

256. Another significant limitation is that some of the patients received other drugs in addition to inhaled treprostinil. For example, of the 11 patients for whom 6MWD data was available, 4 of the patients were also on sildenafil or tadalafil.<sup>467</sup> Each patient was also on an “optimized therap[y] for treatment of baseline lung disease,” which continued throughout the observation period.<sup>468</sup> This limits the ability to discern effects attributable to treprostinil. Dr. Channick’s report ignores this.

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<sup>461</sup> Thomson Reuters Streetevents Edited Transcript UTHR – United Therapeutics Corp to Host Science Day 2018, September 24, 2018 (LIQ\_PH-ILD\_00140569) (“2018 Waxman Tr.”) at -00140611.

<sup>462</sup> *Id.*

<sup>463</sup> *Id.*

<sup>464</sup> *Id.*

<sup>465</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009941.

<sup>466</sup> *Supra* § X.

<sup>467</sup> Faria-Urbina 2018 at -009940, Fig. 3.

<sup>468</sup> *Id.* at 009937.

257. I note that all the comparisons reported in Faria-Urbina 2018 are between at least 3 months (~12 weeks) and baseline data.<sup>469</sup> Faria-Urbina 2018 does not report change scores for 8 weeks and may not report change scores reflecting 12 weeks or even 16 weeks.

258. Finally, Dr. Channick's Report, notes that the Faria-Urbina 2018 "results suggest that 'iTRE is safe in patients with Group 3 PH and evidence of pulmonary vascular remodeling,'" and that "[t]he authors further concluded that inhaled treprostinil was safe in Group 3 PH patients."<sup>470</sup> As noted above, I cannot evaluate whether the authors' conclusions regarding safety and tolerability are justified by the reported findings.<sup>471</sup> However, unlike Dr. Channick, the authors conclusions are expressly and necessarily limited to the patient population to which the chart review was directed: a highly screened sample cohort arrived at by applying inclusion criteria indicating severe PH and/or pulmonary vascular remodeling and exclusion criteria that appear to have excluded higher risk patients.<sup>472</sup> Moreover, as noted above, the chart review's limited sample size and the selection effects leading to that sample size strongly suggest that the reported data are not representative of PH-ILD patients.<sup>473</sup>

259. Dr. Channick's report frequently cites to materials, e.g., depositions from this litigation, in its treatment of Faria-Urbina 2018.<sup>474</sup> Because these materials would not have been available to the POSA, these materials do not support Dr. Channick's positions.

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<sup>469</sup> *Id.* (noting "follow-up  $\leq$  3 months" as exclusion criteria).

<sup>470</sup> Channick Op. Rept. at ¶ 123.

<sup>471</sup> Channick Op. Rept. at ¶ 123; *supra* §§ VII, IX.E.

<sup>472</sup> Faria-Urbina 2018 at -009937.

<sup>473</sup> *Supra* §§ VII, IX.E; Faria-Urbina 2018 at 009936 to 009938.

<sup>474</sup> Channick Op. Rept. ¶¶ 120-123, 125.

## **XII. DR. HILL'S REPORT**

### **A. Purported Personal Observations are Subject to Bias**

260. Section VI of Dr. Hill's report is a catalog of instances of physicians allegedly using inhaled treprostinil off-label in Group 3 PH patients after approval of Tyvaso® in 2009.<sup>475</sup> In support of these clinical decisions, the cited physicians refer to their belief that inhaled treprostinil would improve exercise capacity, or that there were biological reasons to think that it would work in Group 3 patients as well as Group 1 patients, or that patients for whom they had prescribed inhaled treprostinil did better in their experience.<sup>476</sup> Unfortunately, belief, personal experience, and biological plausibility are unreliable guides as to whether, keeping all other aspects of treatment the same, using a drug produces better outcomes than not using it.

261. Medical history is replete with examples of drugs which were widely believed to be effective, with a biologically plausible explanation, and that seemed to be borne out by individual experience that ultimately turned out not to produce better outcomes—or even worse outcomes.

262. Firm belief by some physicians that ivermectin (an anti-parasite drug) or hydroxychloroquine (and anti-malaria drug) effectively prevented or treated COVID-19 led many patients to be treated with those drugs.<sup>477</sup> There was a biological basis to try ivermectin, as it

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<sup>475</sup> 2024-12-20 Expert Report of Dr. Nicholas Hill ("Hill Op. Rept.") at Section VI.

<sup>476</sup> *Id.*

<sup>477</sup> Susanna Naggie et al., *Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19*, 328 JAMA 1595 (2022) ("Naggie 2022") at 1596, 1601-02; Jiuyang Xu & Bin Cao, *Lessons Learnt from Hydroxychloroquine/Azithromycin in Treatment of COVID-19*, 59 Eur. Respiratory J. 2102002 (2022) ("Xu 2022") at 2 ("Retrospective analysis and observational studies may provide timely and useful information, but care must be taken when evaluating such evidence and cross validation from multiple cohorts/studies is optimal. Conclusions drawn from a few or a single cohort, especially when the sample number is limited, may be biased. High level evidence from well-designed, strictly adhered to, and preferably large-scale randomised clinical trials is important for making clinical decisions.").

inhibited growth of the Sars-Cov-2 virus in laboratory experiments.<sup>478</sup> But the “success” of these drugs in the anecdotal experience of individual physicians was refuted in carefully controlled trials, which showed that ivermectin was ineffective at treating or preventing COVID-19.<sup>479</sup> Indeed, both ivermectin and hydroxychloroquine can produce serious side effects.

263. Another example is the case of flecainide (and related drugs) for prevention of sudden cardiac death in patients with certain unstable arrhythmias called premature ventricular contractions (PVCs). It was well established that recurrent PVCs were a risk factor for sudden cardiac death, and the more PVCs, the greater the chance of dying.<sup>480</sup> Flecainide rapidly suppressed PVCs and restored a normal heart rhythm.<sup>481</sup> It became the standard of care for treating patients with these unstable arrhythmias.<sup>482</sup> Doctors believed in the efficacy of flecainide to such an extent that when a randomized clinical trial was being planned to test the efficacy of flecainide, many would not allow their patients to participate on the theory that flecainide was highly effective and that it would be unethical to allow the possibility that their patients might be randomized to receive placebo. In fact, the Cardiac Arrhythmia Suppression Trial (CAST) definitively showed not only that flecainide was not effective at preventing sudden cardiac death, but it also actually *increased* the chance of cardiac death—and by a substantial margin—over placebo.<sup>483</sup> (The same result was found for the related drugs.)

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<sup>478</sup> Naggie 2022 at 1596.

<sup>479</sup> *Id.* at 1601-02; Xu 2022 at 2.

<sup>480</sup> Debra S. Echt et al., *Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo*, 324 N. Eng. J. Med. 781 (1991) (“Echt 1991”) at 781.

<sup>481</sup> *Id.* at 785.

<sup>482</sup> Joel Morganroth et al., *Treatment of Ventricular Arrhythmias by United States Cardiologists: A Survey Before the Cardiac Arrhythmia Suppression Trial Results Were Available*, 65 Am. J. Cardiology 40 (1990) (“Morganroth 1990”) at 42-43.

<sup>483</sup> *Id.* at 44; Echt 1991 at 785-86; David L. Sackett & William M. C. Rosenberg, *On The Need for Evidence-Based Medicine*, 4 Health Econ. 249 (1995) (“Sackett 1995”) at 249.

264. Indeed, the strongly-held belief that inhaled treprostinil was safe and effective in increasing exercise capacity in Group 3 patients was shown not to be the case for Group 3 patients with PH-COPD by the PERFECT study, which showed an increase in serious adverse events as compared to placebo treatment with no indication of improvement in 6MWD.<sup>484</sup>

265. In conclusion, it is my opinion that the purported off-label use of inhaled treprostinil for the treatment of WHO Group 3 PH described in Section VI of Dr. Hill's report would not reasonably convey as of the priority date that the claimed method of treatment works for its intended purpose by improving exercise capacity in PH-ILD patients, and thus it is further my opinion that the alleged off-label use would not render the claimed method ready for patenting or anticipated.

266. Moreover, Dr. Hill's report frequently cites to materials, e.g., depositions from this litigation, in its treatment of this subject matter.<sup>485</sup> Because these materials would not have been available to the POSA, these materials do not support Dr. Channick's positions.

### **XIII. THE ASSERTED CLAIMS OF THE '327 PATENT ARE NOT ANTICIPATED**

#### **A. Faria-Urbina 2018 Does Not Anticipate Claims 1-3, 6, 11, and 15-19 of the '327 Patent.**

267. Dr. Channick's report frequently cites to materials, e.g., depositions from this litigation, in its treatment of anticipation.<sup>486</sup> Because these materials would not have been available to the POSA, these materials do not support Dr. Channick's positions.

#### **1. Claims 1, 11, and 15-16 of the '327 Patent is Not Anticipated by Faria-Urbina 2018.**

##### **a. Claim 1: "A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising administering by inhalation to the patient**

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<sup>484</sup> *Supra* § X.

<sup>485</sup> Hill Op. Rpt. Section VI.

<sup>486</sup> Channick Op. Rept. at ¶¶ 159-160, 163-164.

**having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath.”**

268. Counsel has informed me that the preamble of claim 1 is limiting.<sup>487</sup> Accordingly, a POSA would view claim 1 limited to a “method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease by administering inhaled treprostinil.”<sup>488</sup> I further understand that this limiting preamble is the purpose for which the claimed method must be performed.<sup>489</sup> Claim 1 further requires administering an “effective” amount.<sup>490</sup> This “effective” amount must refer to being effective at improving exercise capacity.<sup>491</sup> The POSA, however, could not perform the claimed method or expect it to be successful without sufficient reliable data.<sup>492</sup> For the reasons explained above, none of the references cited by Dr. Channick alone or combined would provide sufficient data for the POSA to satisfy these requirements of claim 1.<sup>493</sup>

269. As detailed above, Faria-Urbina 2018 fails to disclose any inhaled treprostinil treatment effect.<sup>494</sup> That is, Faria-Urbina 2018 cannot disclose an inhaled treprostinil treatment effect because it reports data generated by a single-arm, single-center, open-label, retrospective chart review.<sup>495</sup> A POSA would understand or a biostatistician like myself would inform a POSA

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<sup>487</sup> Redacted Version of D.I. 123, Joint Claim Construction Brief (“D.I. 127”).

<sup>488</sup> *Supra* § VIII; ’327 Patent; Claim Construction Order (“D.I. 155”).

<sup>489</sup> *Supra* § VIII; ’327 Patent; D.I. 155.

<sup>490</sup> *Supra* § VIII; ’327 Patent; D.I. 155.

<sup>491</sup> *Supra* §§ VII, VIII, IX, X, XI; ’327 Patent; D.I. 155.

<sup>492</sup> *Supra* §§ VII, VIII, IX, X, XI; ’327 Patent; D.I. 155.

<sup>493</sup> *Supra* §§ VII, VIII, IX, X, XI; ’327 Patent; D.I. 155; ’793 Patent; Saggar 2014; Parikh 2016; Agarwal 2015; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>494</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>495</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

that is one of the critical limitations of a single-arm chart review.<sup>496</sup> Comparisons in single-arm studies can only be in the form of change scores—i.e., the differences between patients’ respective baselines and follow-up visits.<sup>497</sup> Tests of statistical significance in change scores in patients that received the same treatment under study (inhaled treprostinil in this chart review) cannot be used to draw inferences about the effectiveness of that treatment. Therefore, a POSA would know or be informed that Faria-Urbina 2018 does not disclose an inhaled treprostinil treatment effect.<sup>498</sup> Accordingly, Faria-Urbina 2018 does not disclose administering inhaled treprostinil to a patient having pulmonary hypertension associated with interstitial lung disease intending to improve exercise capacity.<sup>499</sup>

270. As detailed above, the fact that the chart review Faria-Urbina 2018 reports is also a single-center, open label, retrospective chart review introduces further limitations that a POSA would recognize as further support that Faria-Urbina 2018 does not disclose an inhaled treprostinil treatment effect.<sup>500</sup> The issues arising from these limitations cast doubt on whether, had all the PH-ILD and PH-CPFE patients been evaluated for exercise capacity, there would have been any positive changes at all in exercise capacity.<sup>501</sup> For example, because the study was retrospective and unblinded, the decision whether to conduct a follow-up 6MWD was left to the discretion of

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<sup>496</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>497</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>498</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>499</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>500</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>501</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

the treating physician.<sup>502</sup> Because no account is given as to why half of the study population was excluded from this evaluation, we cannot rule out reasons such as not doing the 6MWD test in patients who were judged unlikely to be able to complete the test, a practice that would skew the results in a favorable direction.<sup>503</sup> Additional bias can result from the practices and motivations of those physicians at the chart review's single site.<sup>504</sup>

271. As detailed above, the POSA would also have reason to believe that Faria-Urbina 2018 suffered from selection bias.<sup>505</sup> For example, 26 of 61 followed patients were omitted from consideration because after initiation of treprostinil therapy they were hospitalized, had a lung transplant, or their condition deteriorated to the extent they required treatment with additional drugs.<sup>506</sup> The reduced exercise capacity of these patients was not taken into account in the analysis, and their omission suggests the reported data is misleadingly optimistic.<sup>507</sup>

272. Similarly, it appears that a substantial fraction of subjects were not on monotherapy.<sup>508</sup> Of the 11 patients with 6MWD data, 4 of them also received a second drug (sildenafil or tadalafil).<sup>509</sup> So any changes seen in 6MWD in this group could have resulted in part

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<sup>502</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>503</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>504</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>505</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>506</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>507</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>508</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>509</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

from the additional treatment as opposed to treprostinil.<sup>510</sup> For this reason, too, the effects on 6MWD in PH-ILD patients treated with inhaled treprostinil reported in the Faria-Urbina 2018 publication cannot be relied upon by a POSA.<sup>511</sup>

273. Also, as noted above, the number of patients assessed that had PH-ILD or CPFE was exceedingly small—only six patients (only 3 had ILD and another 3 had CPFE).<sup>512</sup> A POSA would know or be informed that this population is unrepresentative of the PH-ILD population.<sup>513</sup>

274. For these reasons, Faria-Urbina 2018 does not teach performing a method improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease by administering inhaled treprostinil.<sup>514</sup> Similarly, Faria-Urbina 2018 fails to report or disclose an inhaled treprostinil treatment effect. Consequently, claim 1 of the '327 patent is not anticipated by Faria-Urbina 2018, and claims 11, and 15-16 are not anticipated as they depend from claim 1.<sup>515</sup>

**2. Dependent Claims 2-3, 6, and 17–19 Are Not Anticipated by Faria-Urbina 2018**

**a. Claim 2: “The method of claim 1, wherein said administering provides a statistically significant increase of a 6 minutes walk**

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<sup>510</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>511</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>512</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>513</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>514</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>515</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

**distance in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.”**

275. Claims 2-3 and 17-19 are not anticipated as they depend from claim 1, and claim 1 is not anticipated by Faria-Urbina 2018 as detailed above.<sup>516</sup>

276. Claims 2-3 and 17-19 also recite the following:

- Claim 2: “said administering provides a statistically significant increase of a 6 minutes walk distance”;
- Claim 3: “said administering increases a 6 minutes walk distance of the patient by at least 10 m”;
- Claim 17: “said administering increases a 6 minutes walk distance of the patient by at least 10 m” ;
- Claim 18: “wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m”; and

277. Claim 19: “said administering increases a 6 minutes walk distance of the patient by at least 15 m.”<sup>517</sup>

278. Each of these claims requires that the claimed method’s “administering” step “provide[]” or “increase[]” a parameter.<sup>518</sup> The claims thus do not merely require an increase, they require that the administering cause that increase.<sup>519</sup> Because Faria-Urbina 2018 has limitations

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<sup>516</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>517</sup> *Supra* § VIII; ’327 Patent; D.I. 155.

<sup>518</sup> *Supra* § VIII; ’327 Patent; D.I. 155.

<sup>519</sup> *Supra* § VIII; ’327 Patent; D.I. 155.

preventing a conclusion that the methods described in that article cause the increases, it cannot meet these claims either.<sup>520</sup>

279. That is because, as detailed above, Faria-Urbina 2018 failed to demonstrate any inhaled treprostinil treatment effect, including 6MWD.<sup>521</sup> Faria-Urbina 2018 reported change scores for 6MWD, which achieved statistical significance as detailed above. Yet that analysis cannot demonstrate a treatment effect.<sup>522</sup> As detailed above, observed change scores can arise entirely from other causes beyond the inhaled treprostinil administration.<sup>523</sup> For instance, Faria-Urbina 2018 reports that “[t]herapies related to the underlying lung disease were continued throughout the observation period” and the reported changes could be due to these other treatments instead of due to treprostinil.<sup>524</sup> As detailed above, other possible factors contributing to favorable changes in 6MWD that are unrelated to treprostinil administration include favorable patient selection, other PH drugs added to treprostinil during treatment such as sildenafil or tadalafil, placebo effects, physician or patient expectation, natural disease course, and systematic selection of which treprostinil patients to analyze and which to discard. As a result, Faria-Urbina 2018 fails to teach that the observed changes in 6MWD are *provided by* administering inhaled treprostinil and thus fails to teach that element of claims 2-3 and 17-19.<sup>525</sup>

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<sup>520</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>521</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>522</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>523</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>524</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>525</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

280. Second, statistical comparison of changes in 6MWD among highly selected patients all of whom received inhaled treprostinil may establish that those patients likely had real changes but cannot establish that those changes were a consequence of their common treatment, or that those changes were different from what comparably selected patients not treated with inhaled treprostinil would incur.<sup>526</sup> Consequently, any statistical significance of changes in 6MWD in the selected patients reported by Faria-Urbina 2018 is addressing a different question—and is thus, irrelevant—to a determination whether inhaled treprostinil provides increases in 6MWD as compared to patients not receiving inhaled treprostinil.<sup>527</sup>

281. Third, Faria-Urbina 2018 reports no information about changes in 6MWD after 8 weeks or 12 weeks of administering inhaled treprostinil, as all follow-up assessments of 6MWD were done only in patients with  $\geq 3$  months (13 weeks) follow-up.<sup>528</sup> Moreover, the follow-up period varied from patient-to-patient at the discretion of the treating physician, so the interval from treatment to follow-up could have been as little as 13 weeks in some patients or substantially longer than 16 weeks.<sup>529</sup> As a result, Faria-Urbina 2018 teaches nothing concerning 6MWD after 8, 12, or 16 weeks of treatment, and thus cannot anticipate claims 2-3 and 17-19.<sup>530</sup>

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<sup>526</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material. A randomized, double-blind, placebo-controlled, multi-center study based on substantially more than half a dozen patients would have the ability to determine that question, as the Faria-Urbina 2018 authors recognize in their call for large prospective trials to be conducted.

<sup>527</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>528</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>529</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>530</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

282. For these reasons, Faria-Urbina 2018 does not teach that administering inhaled treprostinil according to the method of claim 1 provides “said administering provides/increases.”<sup>531</sup> As a result, Faria-Urbina 2018 fails to teach that a statistically significant increase in 6MWD is provided by administering inhaled treprostinil and thus fails to teach that element of claims 2-3 and 17-19.<sup>532</sup>

283. Claims 2-3, 17-19 of the ’327 patent are not anticipated by Faria-Urbina 2018.<sup>533</sup>

**b. Claim 6: “The method of claim 1, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.”**

284. Claim 6 is not anticipated by Faria-Urbina 2018 as it depends from claim 1, and claim 1 is not anticipated by Faria-Urbina 2018 as detailed above.<sup>534</sup> As detailed above, a POSA would understand that the “said administering provides” claim language reflects that the “significant reduction of at least one exacerbations of the interstitial lung disease” outcome is also an inhaled treprostinil treatment effect.<sup>535</sup> In this regard, Faria-Urbina 2018 teaches nothing concerning exacerbations and provides no information whatever about “reduction of at least one exacerbations of the interstitial lung disease.”<sup>536</sup> Consequently, Claim 6 of the ’327 patent is not anticipated by Faria-Urbina 2018.<sup>537</sup>

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<sup>531</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>532</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>533</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>534</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1, XIII.A.2.a; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>535</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1, XIII.A.2.a; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>536</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1, XIII.A.2.a; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

<sup>537</sup> *Supra* §§ VII, VIII, IX.E, XI.B.4, XIII.A.1, XIII.A.2.a; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material.

#### XIV. THE ASSERTED CLAIMS OF THE '327 PATENT ARE NOT OBVIOUS

285. Dr. Channick's report frequently cites to materials, e.g., depositions from this litigation, in its treatment of obviousness.<sup>538</sup> Because these materials would not have been available to the POSA, these materials do not support Dr. Channick's positions.

**A. Asserted Claims 9-10 of the '327 Patent Are Not Rendered Obvious by the February 2020 Press Release in Combination with Saggar 2014 Because the POSA Would Not Have a Reasonable Expectation of Success of Arriving at the Claimed Methods.**

286. Saggar 2014 and the February 2020 Press Release fail to teach claims 9 and 10 and a POSA would not have had a reasonable expectation of success of arriving at the claimed methods in view of Saggar 2014 in combination with the February 2020 Press Release.<sup>539</sup> As detailed above, the "said administering provides" and "said administering improves" claim language reflect that the FVC outcomes are also inhaled treprostinil treatment effects.<sup>540</sup> Accordingly, an inhaled treprostinil treatment effect is required by claims 9 and 10.<sup>541</sup> As detailed above, Saggar 2014 fails to disclose this, and the February 2020 Press Release discloses no results covering FVC.<sup>542</sup> As detailed above, Dr. Channick argues that Saggar 2014 and the '327 patent is an apples-to-apples comparison with respect to reported FVC results.<sup>543</sup> Yet the difference between the data reported by Saggar 2014 and the study disclosed in the '327 patent is vast as detailed above.<sup>544</sup> In short, one provides information regarding a change score—that is Saggar 2014 because it is a single-arm study—and one provides data regarding an inhaled treprostinil treatment effect—the '327

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<sup>538</sup> Channick Op. Rep. ¶¶ 218-221.

<sup>539</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Press Release, United Therapeutics Announces *INCREASE* Study of Tyvaso® Meets Primary and All Secondary Endpoints (Feb. 24, 2020) (UTC\_LIQ00063612) ("Feb. 2020 Press Release").

<sup>540</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>541</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>542</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>543</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>544</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

patent.<sup>545</sup> So, the inhaled treprostinil treatment effect with respect to FVC is absent from both Saggar 2014 and the February 2020 Press Release.<sup>546</sup> For at least that reason, claims 9 and 10 are nonobvious over Saggar 2014 and the February 2020 Press Release.<sup>547</sup>

287. Moreover, a POSA would not have had a reasonable expectation of success of arriving at the claimed methods.<sup>548</sup> That is because there would not have been a motivation to combine or reasonable expectation of success at arriving at the claimed methods.<sup>549</sup> As explained above, Saggar 2014 expressly informs the POSA not to rely on the reported FVC data.<sup>550</sup> Saggar 2014 states that “[t]here were no significant changes in PFT parameters following 12 weeks of treprostinil.”<sup>551</sup> Saggar 2014 also states “[i]mportantly, pulmonary function (i.e., degree of PF) remained unaltered during the study and did not likely confound these findings.”<sup>552</sup> These statements from Saggar 2014 speak for themselves.<sup>553</sup> Additionally, there would be no expectation that a clinical trial investigating the impact of a vasodilator on lung function would succeed.<sup>554</sup> In fact, even the INCREASE inventors relegated FVC to a safety outcome measure.<sup>555</sup>

288. In view of the limitations of the Saggar 2014 study detailed above, and the fact that the February 2020 Press Release does not and cannot fill in the deficiencies of Saggar 2014, an inhaled treprostinil treatment effect with respect to FVC is not in the art that Liquidia cites.<sup>556</sup> The

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<sup>545</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>546</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>547</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>548</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>549</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>550</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>551</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>552</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>553</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>554</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>555</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>556</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

POSA would not have been motivated to combine Saggar 2014 with the February 2020 Press Release, and there would not have been a reasonable expectation of success at arriving at the claimed methods.<sup>557</sup> Consequently, the POSA would conclude that Claim 9 and 10 of the '327 patent are nonobvious.<sup>558</sup>

**B. Asserted Claims 1–11 and 14–19 of the '327 Patent Are Not Rendered Obvious by the '793 Patent in Combination with Faria-Urbina 2018.**

**1. Claim 1, 11, and 14-16 of the '327 Patent Is Not Obvious Over the '793 Patent in Combination with Faria-Urbina 2018.**

289. The limitations of Faria-Urbina 2018 are discussed in detail above.<sup>559</sup> As discussed above, the '793 patent does not disclose improved exercise capacity or any of the other claim outcomes, and the '793 patent does not disclose any data concerning exercise capacity in PH-ILD patients.<sup>560</sup> Moreover, the studies disclosed in the '793 patent are entirely distinct from the multi-center, double-blind, randomized, prospective trial that is the INCREASE study.<sup>561</sup>

290. As discussed above, an inhaled treprostinil treatment effect is absent from Faria-Urbina 2018, and an inhaled treprostinil treatment effect is absent from the '793 patent.<sup>562</sup> Accordingly, Claim 1 is not obvious over Faria-Urbina 2018 in combination with the '793 patent.<sup>563</sup> This is at least because improving exercise capacity with inhaled treprostinil is missing

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<sup>557</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>558</sup> *Supra* §§ VII, VIII, IX.B, XI.B.1, X, XIII; Saggar 2014; Feb. 2020 Press Release.

<sup>559</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>560</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>561</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>562</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>563</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

from the cited art, and claims 2-11 and 14-19 should be nonobvious because they depend from claim 1.<sup>564</sup> Yet the treatment effects that correspond to claims 2-10 and 17-19 are not in the art as detailed above either, and thus these claims should be individually nonobvious.<sup>565</sup> The POSA would not have had a reasonable expectation of success in arriving at the claimed methods.<sup>566</sup> In particular there would not have been a reasonable expectation of success conducting the clinical trial required to discover a treatment effect with respect to improved exercise capacity or any of the other claimed outcomes.<sup>567</sup> As noted above, Faria-Urbina 2018 appropriately voiced the limitations of its chart review, advising that the “[r]esults should be interpreted carefully in view of the small sample size.”<sup>568</sup> As I have discussed above, the authors concluded that a “potential role of inhaled PH-specific drugs in Group 3 PH should be further assessed in large prospective studies.”<sup>569</sup> A POSA would also be aware of the very next sentence in which the authors warn: “[u]ntil then, [inhaled treprostinil’s] use in Group 3 PH should be cautiously evaluated in specialized PH Centers, after an individualized assessment and risk-benefit consideration.”<sup>570</sup> A POSA would know or be informed that the next step forward does not come with a reasonable

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<sup>564</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016.

<sup>565</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016.

<sup>566</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016.

<sup>567</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016.

<sup>568</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016.

<sup>569</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016.

<sup>570</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016.

expectation of success.<sup>571</sup> A POSA would not be buoyed by the '793 patent as that patent does not address exercise capacity (or any other claimed outcome) at all and masks PH-ILD data amongst data reported in aggregate.<sup>572</sup> Additionally, the '793 patent only reflects one dose administered during a right heart catheter, offering no relevant guidance to the POSA in that regard.<sup>573</sup>

291. As detailed above, Faria-Urbina 2018 has a number of limitations that render conclusions concerning the results of administering inhaled treprostinil in patients with PH-ILD potentially misleading and speculative at best.<sup>574</sup> Among these limitations are: no comparison to comparable patients who could have been but were not prescribed inhaled treprostinil; conclusions based on an extremely small sample size of only 3 ILD patients and 3 CPFE patients; conclusions concerning exercise capacity (6MWD) are based on only half of the patients considered for data analysis; the authors draw no conclusion concerning any outcomes in PH-ILD patients; and patients that were considered for data analysis had been highly selected from a broader group of PH patients treated with inhaled treprostinil in a manner that would predispose to favorable outcomes.<sup>575</sup> No results are reported on the combined results from the ILD and CPFE patients.<sup>576</sup> Thus, Faria-Urbina 2018 does not disclose a method that, when practiced, improves exercise

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<sup>571</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>572</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>573</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>574</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>575</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>576</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

capacity as compared to not practicing the method.<sup>577</sup> Nor does it do so specifically in patients “having pulmonary hypertension associated with interstitial lung disease” as opposed to pulmonary hypertension of other etiologies such as COPD.<sup>578</sup>

292. The '793 patent does not remedy this deficiency.<sup>579</sup> By a large margin, the majority of patients included in the studies disclosed in the '793 patent were not patients with PH-ILD, and that patent discloses no information whatsoever about exercise capacity in any group of patients, much less PH-ILD patients.<sup>580</sup> Indeed, all the measurements on study subjects disclosed in the '793 patent are taken within 3 hours of a single administration of inhaled treprostinil.<sup>581</sup> Also, all clinical improvements related to exercise capacity cited in the specification of the '327 Patent concern improvements over a period of weeks.<sup>582</sup>

293. The '793 patent discloses no information specifically about PH-ILD patients, and it discloses no information that would address the failings of the 6MWD data disclosed Faria-Urbina 2018.<sup>583</sup> For these reasons, neither reference, alone or in combination, discloses the elements of (a) improving exercise capacity in (b) PH-ILD patients.<sup>584</sup> Consequently, Claim 1 of

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<sup>577</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>578</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>579</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>580</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>581</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>582</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>583</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>584</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

the '327 patent is nonobvious over Faria-Urbina 2018 and the '793 patent. Claims 11 and 14-16 are nonobvious because they depend from claim 1.<sup>585</sup>

**2. Claims 2-3, 7-8, and 17-19 Are Not Obvious Over '793 Patent in Combination with Faria-Urbina 2018.**

294. *Claims 2-3 and 17-19.* Claims 2-3 and 17-19 are not obvious over Faria-Urbina 2018 and the '793 patent because they depend from claim 1, and claim 1 is not obvious over Faria-Urbina 2018 and the '793 patent.<sup>586</sup> Nonetheless, these claims are individually nonobvious. As discussed above, all of these claims require that the claimed methods' "administering" step "provide[]" or "increase[]" a parameter.<sup>587</sup> The claims thus do not merely require an increase, they require that the administering cause that increase.<sup>588</sup> As also discussed above, Faria-Urbina 2018 has limitations preventing a conclusion that any methods disclosed therein cause the increases.<sup>589</sup> That is because, as detailed above, Faria-Urbina 2018 failed to demonstrate *any* inhaled treprostinil treatment effect, including 6MWD; any statistical significance of changes in 6MWD in the reported by Faria-Urbina 2018 is addressing a different question than claims 2-3 and 17-19; and Faria-Urbina 2018 teaches nothing concerning 6MWD after 8, 12, or 16 weeks of treatment.<sup>590</sup>

295. As discussed above, the '793 patent masks any PH-ILD data by presenting results in aggregate, discloses no information beyond 180 minutes, and discloses nothing concerning

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<sup>585</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>586</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285 XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>587</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285 XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>588</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285 XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>589</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285 XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>590</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285 XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

6MWD.<sup>591</sup> Therefore, the '793 patent does not remedy the deficiencies in Faria-Urbina 2018.<sup>592</sup>

As discussed above, Faria-Urbina 2018 would not provide a POSA a reasonable expectation of success at obtaining the claimed methods, and the '793 patent does not cure this deficiency.<sup>593</sup>

296. Consequently, Claims 2-3 and 17-19 of the '327 patent are not rendered obvious by Faria-Urbina 2018 in combination with the '793 patent.<sup>594</sup>

297. *Claims 7-8.* Claims 7-8 are not obvious over Faria-Urbina 2018 and the '793 patent because they depend from claim 1, and claim 1 is not obvious over Faria-Urbina 2018 and the '793 patent. Nonetheless, these claims are individually nonobvious.<sup>595</sup> As detailed above, a POSA would understand that the “said administering provides” claim language reflects that the “statistically significant reduction of clinical worsening events due to the interstitial lung disease” outcome is also an inhaled treprostinil treatment effect.<sup>596</sup> As discussed above, neither Faria-Urbina 2018 nor the '793 patent teach clinical worsening events due to the interstitial lung disease.<sup>597</sup> As detailed above, neither reference teaches an inhaled treprostinil treatment effect with respect to clinical worsening events due to the interstitial lung disease.<sup>598</sup> As detailed above, a

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<sup>591</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>592</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>593</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>594</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>595</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>596</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>597</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>598</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

POSA would not have a reasonable expectation of success of arriving at the claimed methods.<sup>599</sup> That is at least because a POSA would not expect treprostinil to have a treatment effect with respect to interstitial lung disease.<sup>600</sup> Consequently, claims 7 and 8 of the '327 patent are not rendered obvious by Faria-Urbina 2018 in combination with the '793 patent.<sup>601</sup>

**C. Asserted Claims 4-5, 6, and 9-10 of the '327 patent are not rendered obvious by Faria-Urbina 2018 in combination with the '793 patent and Saggar 2014.**

298. *Claims 4 and 5.* Claims 4-5 are not obvious over Faria-Urbina 2018, Saggar 2014, and the '793 patent as they depend from claim 1, and claim 1 is not obvious over Faria-Urbina 2018, Saggar 2014, and the '793 patent.<sup>602</sup> Claim 1 is not obvious over Faria-Urbina 2018, Saggar 2014, and the '793 patent because Saggar 2014 does not cure the deficiencies Faria-Urbina 2018, and the '793 patent combination.<sup>603</sup> For example, Saggar 2014 does not disclose inhaled treprostinil.<sup>604</sup> Moreover, as detailed above, Saggar 2014 fails to disclose a parenteral treprostinil treatment effect because it too is a single-arm analysis and the study's other features—open label, single-center, small sample size—further evidence that Saggar 2014 does not disclose a parenteral treprostinil treatment effect.<sup>605</sup>

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<sup>599</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>600</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>601</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B.1; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016.

<sup>602</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016; Saggar 2014.

<sup>603</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016; Saggar 2014.

<sup>604</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016; Saggar 2014.

<sup>605</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016; Saggar 2014.

299. Yet claims 4 and 5 are individually nonobvious.<sup>606</sup> As detailed above, a POSA would understand that the “said administering provides” and “said administering reduces” claim language reflects that the “plasma concentration of NT-proBNP” outcome is also an inhaled treprostinil treatment effect.<sup>607</sup> In this regard, neither Faria-Urbina 2018 nor the ’793 patent teach anything regarding NT-proBNP.<sup>608</sup> Saggar 2014 is also deficient, failing to teach inhaled treprostinil and NT-proBNP.<sup>609</sup> Moreover, Saggar 2014 as detailed above does not teach a parenteral treprostinil treatment effect.<sup>610</sup> Accordingly, neither Faria-Urbina 2018, the ’793 patent, nor Saggar 2014 teach all limitations of claim 4-5.<sup>611</sup> Moreover there would not be a reasonable expectation of success that combining these three references would permit a POSA to arrive at the claimed methods.<sup>612</sup>

300. *Claim 6.* None of Faria-Urbina 2018, the ’793 patent, or Saggar 2014 disclose any information about exacerbations of the interstitial lung disease.<sup>613</sup> Moreover, a POSA would not

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<sup>606</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285 XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016; Saggar 2014.

<sup>607</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285 XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016; Saggar 2014.

<sup>608</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285 XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016; Saggar 2014.

<sup>609</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285 XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016; Saggar 2014.

<sup>610</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285 XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016; Saggar 2014.

<sup>611</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285 XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016; Saggar 2014.

<sup>612</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285 XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016; Saggar 2014.

<sup>613</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII,285 XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; ’793 Patent; Parikh 2016; Saggar 2014.

have a reasonable expectation of success in combining Faria-Urbina 2018, the '793 patent, and Saggar 2014 to arrive at the methods of Claim 6 of the '327 patent.<sup>614</sup>

301. *Claims 9 and 10.* Saggar 2014 discloses no statistically significant change in FVC nor any specific volume change in FVC, which teaches away from claims 9-10.<sup>615</sup> In addition, Faria-Urbina 2018 reports *reduced* percent predicted FVC, which also teaches away from claims 9-10. Also, as detailed above, there would be no reasonable expectation of success to achieve an inhaled treprostinil treatment effect with respect to the interstitial lung disease.<sup>616</sup> Dependent claims 4, 5, 6, 9, and 10 are not obvious over Faria-Urbina 2018 in combination with the '793 patent and Saggar 2014.<sup>617</sup>

**D. Asserted Claims 1–11 and 14–19 of the '327 Patent Are Not Rendered Obvious by the '793 Patent in Combination with Agarwal 2015.**

**1. Claim 1, 11, and 14–16 of the '327 Patent Is Not Obvious Over the '793 Patent in Combination with Agarwal 2015.**

302. As detailed above, Agarwal 2015 fails to disclose an inhaled treprostinil treatment effect.<sup>618</sup> That is Agarwal 2015 cannot disclose an inhaled treprostinil treatment effect because it reports data generated by single-arm, single-center, open-label, retrospective chart review.<sup>619</sup> A POSA would understand or a biostatistician like myself would inform a POSA that this is one of

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<sup>614</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285 XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016; Saggar 2014.

<sup>615</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285 XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016; Saggar 2014.

<sup>616</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285 XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Parikh 2016; Saggar 2014.

<sup>617</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285 XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Saggar 2014; '327 patent at 54:23-33, 54:42-49.<sup>617</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285-XIV.B; Faria-Urbina 2018; Faria-Urbina 2018 Supplementary Material; '793 Patent; Saggar 2014; '327 patent at 54:23-33, 54:42-49.

<sup>618</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285-XIV.C; *see* Agarwal 2015 at \_009828.

<sup>619</sup> *Id.*

the critical limitations of a single-arm chart review.<sup>620</sup> A single-arm study can only produce change scores—i.e., the differences between patients’ respective baselines and follow-up visits.<sup>621</sup> Tests of statistical significance in change scores in patients that received the same treatment under study (inhaled treprostinil in this chart review) cannot be used to draw inferences about the effectiveness of that treatment.<sup>622</sup> Therefore a POSA would know or be informed that Agarwal 2015 does not disclose an inhaled treprostinil treatment effect.<sup>623</sup> Accordingly, Agarwal 2015 does not disclose administering inhaled treprostinil to a patient having pulmonary hypertension associated with interstitial lung disease intending to improve exercise capacity.<sup>624</sup>

303. As detailed above, the fact that the chart review Agarwal 2015 reports is also a single-center, open label, retrospective chart review introduces further limitations that a POSA would recognize as further support that Agarwal 2015 does not disclose an inhaled treprostinil treatment effect.<sup>625</sup> The issues arising from these limitations cast doubt on whether, had all the PH-ILD and PH-CPFE patients been evaluated for exercise capacity, there would have been any positive changes at all in exercise capacity.<sup>626</sup>

304. For example, about 26% (9/35) of the followed patients were not included in the outcome assessments because they discontinued therapy for the reasons detailed above.<sup>627</sup> Those patients that were excluded appear to have been systematically sicker than those ultimately included in the reported results, suggesting that the reported change scores are too optimistic.<sup>628</sup>

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<sup>620</sup> *Id.*  
<sup>621</sup> *Id.*  
<sup>622</sup> *Id.*  
<sup>623</sup> *Id.*  
<sup>624</sup> *Id.*  
<sup>625</sup> *Id.*  
<sup>626</sup> *Id.*  
<sup>627</sup> *Id.*  
<sup>628</sup> *Id.*

As noted above, only 21 patients had data on change in 6MWD, an unknown number of which had PH-ILD.<sup>629</sup> Sample sizes for other outcome measures such as WHO functional class and BDI were not reported.<sup>630</sup> As noted above, such a small sample in and of itself strongly suggests that the data reported by Agarwal 2015 are not representative of PH-ILD patients.<sup>631</sup>

305. There's also concern that the chart review's open label design impacted the reported data, especially since the chart review was carried out at a single site.<sup>632</sup>

306. Additionally, while not noted in Agarwal 2015, a March 2015 presentation given by Dr. Waxman, one of the authors of Agarwal 2015, indicates that 15 patients received dual therapy for at least a portion of the study, and "tolerated the addition of a systemic pulmonary vasodilator (PDE5i)."<sup>633</sup>

307. Agarwal 2015 does not disclose improved exercise capacity as compared to placebo.<sup>634</sup> Even the 6MWD data that Agarwal 2015 reports cannot be reliably said to represent the results in PH-ILD patients.<sup>635</sup> This is partly because the PH-ILD patients were not clearly broken out in the report, and this is in part because patients in whom the drug was ineffective were never measured for changes in 6MWD and were not included in the reported results.<sup>636</sup>

308. For these reasons, Agarwal 2015 does not teach performing a method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung

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<sup>629</sup> *Id.*

<sup>630</sup> *Id.*

<sup>631</sup> *Id.*

<sup>632</sup> *Id.*

<sup>633</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C; March 2015 Presentation at 082508.

<sup>634</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C; Agarwal 2015 at 009828.

<sup>635</sup> *Id.*

<sup>636</sup> *Id.*; Agarwal 2015; '793 patent; Parikh 2016.

disease by administering inhaled treprostinil.<sup>637</sup> Similarly, Agarwal 2015 fails to report or disclose an inhaled treprostinil treatment effect.<sup>638</sup>

309. As detailed above, the '793 patent does not disclose any data concerning exercise capacity in PH-ILD patients.<sup>639</sup> Moreover, the studies disclosed in the '793 patent are entirely distinct from the multi-center, double-blind, randomized, prospective trial that is in the INCREASE study.<sup>640</sup>

310. As discussed above, an inhaled treprostinil treatment effect is absent from Agarwal 2015.<sup>641</sup> And, as discussed above an inhaled treprostinil treatment effect is absent from the '793 patent.<sup>642</sup> Accordingly, Claim 1 is not obvious over Agarwal 2015 and the '793 patent.<sup>643</sup> This is at least because improving exercise capacity with inhaled treprostinil is missing from the cited art, and claims 2-11 and 14-19 should be nonobvious because they depend from claim 1.<sup>644</sup> Yet inhaled treprostinil treatment effects corresponding to claims 2-10 and 17-19 are not in the art either as detailed above, and thus these claims are individually nonobvious.<sup>645</sup>

311. The POSA would not have had a reasonable expectation of success in arriving at the claimed methods.<sup>646</sup> There was no expectation of success that the clinical trial required to demonstrate an inhaled treprostinil treatment effect with respect to improved exercise capacity or

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<sup>637</sup> *Id.*

<sup>638</sup> *Id.*

<sup>639</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C; '793 patent at 009772-009796.

<sup>640</sup> *Id.*

<sup>641</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C; Agarwal 2015 at 009828.

<sup>642</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C; *see also* '793 patent at 009772-009796.

<sup>643</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C; Agarwal 2015 at 009828; '793 patent at 009772-009796; '327 patent at 54:6-14.

<sup>644</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C; '327 patent at 54:15-49, 54:57-55:9.

<sup>645</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C; '327 patent at 54:15-49, 55:1-9.

<sup>646</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C.

any of the other claimed outcomes.<sup>647</sup> Agarwal 2015, which a POSA would recognize a merely an abstract, concludes “[a] prospective trial is indicated.”<sup>648</sup> A POSA would know or be informed that this step does not come with a reasonable expectation of success.<sup>649</sup> Moreover, a POSA would not be buoyed by the ’793 patent—a patent that does not address exercise capacity (or any other claimed outcome) at all and for which any PH-ILD data is masked amongst data reported in aggregate.<sup>650</sup> A POSA would also understand that the ’793 patent only reflects data from one dose administered during a right heart catheter. Therefore, a POSA would find no guidance relevant or otherwise in the ’793 patent.<sup>651</sup>

312. As detailed above, claim 1 of the ’327 patent is not obvious over Agarwal 2015 in combination with the ’793 patent, and claims 11 and 15-16 are not obvious as they depend from claim 1.<sup>652</sup>

## 2. Dependent Claims 2-3, 7-8, and 17-19 Are Not Obvious Over the ’793 Patent in Combination with Agarwal 2015.

313. *Claims 2-3 and 17–19.* Claims 2-3 and 17-19 are not obvious over Agarwal 2015 and the ’793 patent because they depend from claim 1, and claim 1 is not obvious over Agarwal 2015 and the ’793 patent.<sup>653</sup> Nonetheless, these claims are individually nonobvious. As discussed above, all of these claims require that the claimed methods’ “administering” step “provide[]” or

<sup>647</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C; *see also* Agarwal 2015 at 009828.

<sup>648</sup> *Id.*

<sup>649</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285 XIV.B, XIV.C.

<sup>650</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C; ’793 patent at 009772-009796.

<sup>651</sup> *Id.*

<sup>652</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C; Agarwal 2015 at 009828; ’793 patent at 009772-009796; ’327 patent at 54:6-14, 54:50-51, 54:61-67.

<sup>653</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C, XIV.D.1; Agarwal 2015 at 009828; ’793 patent at 009772-009796; ’327 patent at 54:15-22, 55:1-9.

“increase[.]” a parameter.<sup>654</sup> The claims thus do not merely require an increase, they require that the administering cause that increase.<sup>655</sup> As also discussed above, Agarwal 2015 has limitations preventing a conclusion that the methods described in that abstract cause the increases.<sup>656</sup> That is because, as detailed above, Agarwal 2015 failed to demonstrate *any* inhaled treprostinil treatment effect, including 6MWD.<sup>657</sup> Therefore any statistical significance of changes in 6MWD in the selected patients reported by Agarwal 2015 is addressing a different question than claims 2-3 and 17-19; and Agarwal 2015 teaches nothing concerning 6MWD after 8, 12, or 16 weeks of treatment.<sup>658</sup>

314. Consequently, Claims 2-3, and 17–19 of the ’327 patent are not obvious over Agarwal 2015 in combination with the ’793 patent.<sup>659</sup>

315. *Claims 7-8.* Claims 7-8 are not obvious over Agarwal 2015 and the ’793 patent because they depend from claim 1, and claim 1 is not obvious over Agarwal 2015 and the ’793 patent.<sup>660</sup> Nonetheless, these claims are individually nonobvious. As detailed above, a POSA would understand that the “said administering provides” claim language reflects that the “statistically significant reduction of clinical worsening events due to the interstitial lung disease” outcome is also an inhaled treprostinil treatment effect.<sup>661</sup> As discussed above, neither Agarwal

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<sup>654</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B, XIV.C, XIV.D.1; ’327 patent at 54:15-22, 55:1-9.

<sup>655</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B, XIV.C, XIV.D.1; ’327 patent at 54:15-22, 55:1-9.

<sup>656</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C, XIV.D.1; Agarwal 2015 at 009828.

<sup>657</sup> *Id.*

<sup>658</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C, XIV.D.1; *see also* Agarwal 2015 at 009828; ’327 patent at 54:15-22, 55:1-9.

<sup>659</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B, XIV.C, XIV.D.1; Agarwal 2015 at 009828; ’793 patent at 009772-009796; ’327 patent at 54:15-22, 55:1-9.

<sup>660</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.C, XIV.D.1; Agarwal 2015 at 009828; ’793 patent at 009772-009796; ’327 patent at 54:34-41.

<sup>661</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C, XIV.D.1; ’327 patent at 54:34-36.

2015 nor the '793 patent teach clinical worsening events due to the interstitial lung disease.<sup>662</sup> As detailed above, neither reference teaches an inhaled treprostinil treatment effect with respect to clinical worsening events due to the interstitial lung disease.<sup>663</sup> As detailed above, a POSA would not have had a reasonable expectation of success of arriving at the claimed methods.<sup>664</sup> That is at least because a POSA would not expect treprostinil to have a treatment effect with respect to interstitial lung disease.<sup>665</sup> Consequently, claims 7 and 8 of the '327 patent are not rendered obvious by Agarwal 2015 in combination with the '793 patent.<sup>666</sup>

**E. Asserted Claims 4-5, 6, and 9-10 of the '327 patent are not rendered obvious by the '793 patent in combination with Agarwal 2015 and Saggar 2014.**

316. *Claims 4 and 5.* Claims 4-5 are not obvious over Agarwal 2015, Saggar 2014, and the '793 patent as they depend from claim 1, and claim 1 is not obvious over Agarwal 2015, Saggar 2014, and the '793 patent.<sup>667</sup> Claim 1 is not obvious over Agarwal 2015, Saggar 2014, and the '793 patent because Saggar 2014 does not cure the deficiencies Agarwal 2015, and the '793 patent combination.<sup>668</sup> For example, Saggar 2014 does not disclose inhaled treprostinil.<sup>669</sup> Moreover, as detailed above, Saggar 2014 fails to disclose a parenteral treprostinil treatment effect because it too is a single-arm analysis and the study's other features—open label, single-center, small sample

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<sup>662</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C, XIV.D.1; Agarwal 2015 at 009828; '793 patent at 009772-009796.

<sup>663</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C, XIV.D.1; Agarwal 2015 at 009828; '793 patent at 009772-009796; Parikh 2016 at 010599-010610.

<sup>664</sup> *Id.*

<sup>665</sup> *Id.*

<sup>666</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.C, XIV.D.1; Agarwal 2015 at 009828; '793 patent at 009772-009796; '327 patent at 54:34-41.

<sup>667</sup> *Supra* §§ VII, VIII, IX, XI.B, X, XIII, 285XIV.B, XIV.C, XIV.D; Agarwal 2015 at 009828; '793 patent at 009772-009796; Parikh 2016 at 010599-010610; Saggar 2014 at 00000226-00000246; '327 patent at 54:6-14, 54:23-30.

<sup>668</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.D; Agarwal 2015 at 009828; '793 patent at 009772-009796; Parikh 2016 at 010599-010610; Saggar 2014 at 00000226-00000246; '327 patent at 54:6-14.

<sup>669</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285-XIV.D; Saggar 2014 at 00000226-00000246.

size—further evidence that Saggar 2014 does not disclose a parenteral treprostinil treatment effect.<sup>670</sup>

317. Yet claims 4 and 5 are individually nonobvious. As detailed above, a POSA would understand that the “said administering provides” and “said administering reduces” claim language reflects that the “plasma concentration of NT-proBNP” outcome is also an inhaled treprostinil treatment effect.<sup>671</sup> In this regard, neither Agarwal 2015 nor the ’793 patent teach anything regarding NT-proBNP.<sup>672</sup> Saggar 2014 is also deficient, failing to teach inhaled treprostinil and NT-proBNP.<sup>673</sup> Moreover, Saggar 2014 as detailed above does not teach a parenteral treprostinil treatment effect.<sup>674</sup> Accordingly, neither Agarwal 2015, the ’793 patent, nor Saggar 2014 teach all limitations of claim 4-5.<sup>675</sup> Moreover, there would not be a reasonable expectation of success that combining these three references would permit a POSA to arrive at the claimed methods.<sup>676</sup>

318. *Claim 6.* None of Agarwal 2015, the ’793 patent, or Saggar 2014 disclose any information about exacerbations of the interstitial lung disease.<sup>677</sup> Moreover, a POSA would not have a reasonable expectation of success in combining Agarwal 2015, the ’793 Patent, and Saggar 2014 to arrive at the methods of Claim 6 of the ’327 patent.<sup>678</sup>

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<sup>670</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285-XIV.D; Saggar 2014 at 00000226-00000246.

<sup>671</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285-XIV.D; Agarwal 2015 at 009828; ’793 patent at 009772-009796; ’327 patent at 54:23-25, 54:27-28.

<sup>672</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, XIV.D285; Agarwal 2015 at 009828; ’793 patent at 009772-009796.

<sup>673</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.D; Saggar 2014 at 00000226-00000246.

<sup>674</sup> *Id.*

<sup>675</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.D; Agarwal 2015 at UTC\_PH-ILD\_009828; ’793 patent at 009772-009796; Parikh 2016 at 010599-010610; Saggar 2014 at 00000226-00000246; ’327 patent at 54:23-30.

<sup>676</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285XIV.D; *see also* Agarwal 2015 at 009828; ’793 patent at 009772-009796; Parikh 2016 at 010599-010610; Saggar 2014 at 00000226-00000246.

<sup>677</sup> *Id.*

<sup>678</sup> *Id.*; ’327 patent at 54:31-33.

319. *Claims 9 and 10.* As detailed above, Saggar 2014 teaches away from claims 9-10.

In addition, Agarwal 2015 discloses nothing concerning changes in FVC, over its 6-month follow-up period.<sup>679</sup> Also as detailed above, there would be no reasonable expectation of success to achieve an inhaled treprostinil treatment effect with respect to the interstitial lung disease.<sup>680</sup> Dependent claims 4, 5, 6, 9, and 10 are not obvious over Agarwal 2015 in combination with the '793 patent and Saggar 2014.<sup>681</sup>

## XV. CONCLUSIONS

320. As set forth above, it is my opinion that:

- Dr. Channick's conclusions concerning what the prior art teaches are based on a severe misunderstanding of clinical study design that ignores fundamental limitations to what the prior art can demonstrate to a POSA. Based on the POSA's medical education and training the POSA would understand that these limitations prevent the hindsight driven conclusions that Dr. Channick reaches.
- Faria-Urbina 2018, Agarwal 2015, Saggar 2014, and Parikh 2016 each only report uncontrolled, i.e., single-arm, analyses, and thus are statistically unable to demonstrate any treatment effect resulting from administering inhaled treprostinil.
- A POSA would know or be informed by a biostatistician that the respective single-arm studies reported by Faria-Urbina 2018, Agarwal 2015, Saggar 2014, and Parikh 2016 suffer from severe undersampling, and thus the data and results generated by each study lacks generalizability to the analyzed patient populations, which was expressly not even the pulmonary hypertension associated with interstitial lung disease population in the respective studies reported by Faria-Urbina 2018, Agarwal 2015, and Parikh 2016.
- A POSA would know or be informed by a biostatistician that the respective single-arm studies reported by Faria-Urbina 2018, Agarwal 2015, Saggar 2014, and Parikh 2016 suffered from bias, especially selection bias, and thus the data produced from these studies lack reliability and generate overstated results.

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<sup>679</sup> Agarwal 2015 at 009828.

<sup>680</sup> *Supra* §§ VII-VIII, IX, XI.B, X, XIII, 285-XIV.D; Agarwal 2015 at 009828; '793 patent at 009772-009796; Parikh 2016 at 010599-010610; Saggar 2014 at 0000226-00000246.

<sup>681</sup> *Id.*; '327 patent at 54:23-33, 54:42-49.

- Faria-Urbina 2018, Agarwal 2015, Saggar 2014, and Parikh 2016 would not have demonstrated to prescribing physicians as of the priority date that inhaled treprostinil improves exercise capacity in patients with PH-ILD.
- Faria-Urbina 2018 does not anticipate claims 1-3, 6, 11, and 15-19 of the '327 patent at least because it is not statistically possible and because the data and results it produced lack generalizability and reliability and are overstated due at least to selection bias.
- The February 2020 Press Release in combination with Saggar 2014 does not render claims 9-10 of the '327 patent obvious at least because it is not statistically possible for Saggar 2014 to demonstrate an inhaled treprostinil treatment effect with respect to FVC, and because the data and results it produced lack generalizability and reliability, and are overstated due at least to selection bias, and because the '793 patent cannot cure these deficiencies, and because a POSA would not have a reasonable expectation of success that the type of studies necessary to demonstrate an inhaled treprostinil treatment effect would do so.
- The '793 patent in combination with Faria-Urbina 2018 does not render claims 1-11 and 14-19 of the '327 patent obvious at least because it is not statistically possible for Faria-Urbina 2018 to demonstrate an inhaled treprostinil treatment effect and because the data and results it produced lack generalizability and reliability, and are overstated due at least to selection bias, and because the '793 patent cannot cure these deficiencies, and because a POSA would not have a reasonable expectation of success that the type of studies necessary to demonstrate an inhaled treprostinil treatment effect would do so.
- Faria-Urbina 2018 in combination with the '793 patent and Saggar 2014 does not render claims 4, 5, 6, 9, and 10 of the '327 patent obvious at least because it is not statistically possible for Faria-Urbina 2018 or Saggar 2014 to demonstrate an inhaled treprostinil treatment effect and because the data and results each produced lack generalizability and reliability, and are overstated due at least to selection bias, and because the '793 patent cannot cure these deficiencies, and because a POSA would not have a reasonable expectation of success that the type of studies necessary to demonstrate an inhaled treprostinil treatment effect would do so.
- The '793 patent in combination with Agarwal 2015 does not render claims 1-11 and 14-19 of the '327 patent obvious at least because it is not statistically possible for Agarwal to demonstrate an inhaled treprostinil treatment effect and because the data and results it produced lack generalizability and reliability, and are overstated due at least to selection bias, and because the '793 patent cannot cure these deficiencies, and because a POSA would not have a reasonable expectation of success that the type of studies necessary to demonstrate an inhaled treprostinil treatment effect would do so.
- The '793 patent in combination with Agarwal 2015 and Saggar 2014 does not render claims 4, 5, 6, 9, and 10 of the '327 patent obvious at least because it is not

statistically possible for Agarwal 2015 or Saggar 2014 to demonstrate an inhaled treprostinil treatment effect and because the data and results each produced lack generalizability and reliability, and are overstated due at least to selection bias, and because the '793 patent cannot cure these deficiencies, and because a POSA would not have a reasonable expectation of success that the type of studies necessary to demonstrate an inhaled treprostinil treatment effect would do so.

I declare under penalty of perjury that the foregoing is true and correct.

DATED: 23 January 2025

Ronald A. Thisted

**Ronald A. Thisted, Ph.D.**

# EXHIBIT A

# **Ronald A. Thisted**

*December 2024*

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- Education: Ph.D. (Statistics) Stanford University, 1977.  
M.S. (Statistics) Stanford University, 1973.  
B.A. (Mathematics, Philosophy) Pomona College, 1972. Magna cum laude
- Professional: *All at the University of Chicago:*  
2018– Professor Emeritus, Departments of Statistics and Public Health Sciences and the College  
2014–2018 Vice-Provost, Academic Affairs  
2009–2018 Member, Committee on Clinical and Translational Science  
2007–2014 Director, Population Sciences, Institute for Translational Medicine  
2005–2018 Member, Center for Cognitive and Social Neuroscience  
2001–2008 Member, Institute for Mind and Biology  
2000–2014 Director, Biostatistics Core Facility, University of Chicago Cancer Research Center  
1999–2012 Chairman, Department of Health Studies (now Public Health Sciences)  
1999–2012 Co-Director, Clinical Research Training Program  
1996–2018 Professor, Department of Public Health Sciences (Health Studies until 2014)  
1993–1998 Co-Director, Robert Wood Johnson Clinical Scholars Program  
1993–2018 Professor, Committee on Clinical Pharmacology and Pharmacogenomics  
1992–2018 Professor, Departments of Statistics, Anesthesia & Critical Care, and the College  
1989–1992 Associate Professor, Department of Anesthesia and Critical Care  
1982–1992 Associate Professor, Department of Statistics and the College  
1979–1982 Leonard Jimmie Savage Assistant Professor, Department of Statistics and the College  
1976–1982 Assistant Professor, Department of Statistics and the College
- Honors: Phi Beta Kappa, Pomona College, 1972.  
Sigma Xi, The University of Chicago, 1977.  
The Llewellyn John and Harriet Manchester Quantrell Award for Excellence in Undergraduate Teaching, 1981.  
Gold Key Award, University of Chicago Biological Sciences, 2018.
- Professional Societies:  
American Association for the Advancement of Science (Elected Fellow, 1992)  
1994–1997 Electorate Nominating Committee, Section on Statistics  
American Statistical Association (Elected Fellow, 1988)  
1987–1989 Section on Statistical Graphics, Chair (1988)  
Association for Computing Machinery  
International Biometric Society, ENAR  
Institute of Mathematical Statistics  
1989–1993, 1999–2002 Management Committee, *Current Index to Statistics*  
Royal Statistical Society (Fellow)  
Society for Industrial and Applied Mathematics, (Visiting Lecturer, 1979–80) –2024
- Editorial: *Computing Reviews*, Reviewer (1978–1987).  
*J American Statistical Assoc*, Associate Editor (1979–1985, 1987–1988).  
*SIAM J Scientific and Statistical Computing*, Editorial Board (1983–1985).  
*ACM Trans on Math Software*, Associate Editor (1990–1992).  
*Current Index to Statistics*, Database Ed. (1994); Managing Ed. (1995); Editor (1996–1998).

## Selected Publications

### Books

- [1] *Elements of Statistical Computing: Numerical Computation*. Chapman & Hall: London. 1988.
- [2] The Chicago Social Brain Network. *Invisible Forces and Powerful Beliefs: Gravity, Gods, and Minds*. FT Press Science: Upper Saddle River, NJ. 2010.

### Original Articles

- [2] “The Prediction of Homicide with the Rorschach” (D Lester, J Kendra, R Thisted, W Perdue). *J. Clinical Psych.*, **31**, (1976), 752.
- [3] “Estimating the Number of Unseen Species: How Many Words Did Shakespeare Know?” (B Efron, RA Thisted). *Biometrika*, **63**, (1976), 435-447.
- [4] *Ridge Regression, Minimax Estimation, and Empirical Bayes Methods*. Ph.D. Thesis, Department of Statistics, Stanford University (1976).
- [5] “Prediction of Homicide and Suicide: A Test in a Healthy Risk-Taking Group” (D Lester, JM Kendra, RA Thisted). *Perceptual and Motor Skills*, **44**, (1977), 222.
- [6] “Teaching Statistical Computing Using Computer Packages” (with Discussion), *The American Statistician*, **33**, (1979), 27–35.
- [7] “User Documentation and Control Language I: Evaluation and Comparison of Statistical Computer Packages.” *Computers & Education*, **3**, (1979), 135–141.
- [8] “Predicting a Multitude of Time Series” (RA Thisted, WE Wecker). *Journal of the American Statistical Association*, **75**, (1980), 81–86.
- [9] “Lactic Acidemia in Reye’s Syndrome” (JH Tonsgard, PR Huttenlocher, RA Thisted). *Pediatrics*, **69**, (1982), 64–69.
- [10] “Maximum Likelihood Estimation of Isotonic Modal Regression” (T Sager, R Thisted). *Annals of Statistics*, **10**, (1982), 690–707.
- [11] “Safety and Efficacy of Chymopapain (Chymodiactin) in Herniated Nucleus Pulposus With Sciatica: Results of a Randomized, Double-blind Study” (MJ Javid, EJ Nordby, LT Ford, WJ Hejna, WW Whisler, C Burton, DK Millett, LL Wiltse, EH Widell Jr, RJ Boyd, StE Newton, RA Thisted). *Journal of the American Medical Association*, **249:18**, (1983), 2489–2494.
- [12] “A Statistical Study of Mate Choice: Sexual Selection in a Plethodontid Salamander (*Desmognathus Ochrophæus*),” (L Houck, SJ Arnold, RA Thisted). *Evolution*, **39**, (1985), 370–386.
- [13] “Chymodiactin in Patients with Herniated Lumbar Intervertebral Disc(s): An Open-Label, Multicenter Study,” (DJ McDermott, K Agre, M Brim, FJ Demma, J Nelson, RR Wilson, RA Thisted). *Spine*, **10**, (1985), 242–249.
- [14] “Decreased Incidence and Mortality of Anaphylaxis to Chymopapain,” (J Moss, MF Roizen, EJ Nordby, RA Thisted, JL Apfelbaum, BD Schreider, DJ McDermott). *Anesthesia and Analgesia*, **64**, (1985), 1197–1201.
- [15] “Computing Environments for Data Analysis,” (with Discussion), *Statistical Science*, **1**, (1986), 259–275.
- [16] “Did Shakespeare Write a Newly-Discovered Poem?” (R Thisted, B Efron). *Biometrika*, **74**, (1987), 445–455.
- [17] “Cervical Injury in Head Trauma,” (GL Neifeld, JG Keene, G Hevesy, J Leikin, A Proust, RA Thisted). *Journal of Emergency Medicine*, **6**, (1988), 203–207.
- [18] “Patient-Applied Podofilox for Treatment of Genital Warts,” (KR Beutner, MA Conant, AE Friedman-Kien, M Illeman, NN Artman, RA Thisted, DH King). *Lancet*, (1989, April 15), 831–834.
- [19] “Using a National Health Care Data Base to Determine Surgical Complications in Community Hospitals: Lumbar Discectomy as an Example” (L Ramirez, R Thisted). *Neurosurgery*, **25**, (1989), 218–225.

- [20] “Complications and Demographic Characteristics of Patients Undergoing Lumbar Discectomy in Community Hospitals,” (L Ramirez, R Thisted). *Neurosurgery*, **25**, (1989), 226–231.
- [21] “Increased Risk for Gestational Diabetes Mellitus Associated with Insulin Receptor and Insulin-like Growth Factor II Restriction Fragment Length Polymorphisms” (C Ober, KS Xiang, RA Thisted, KA Intovina, CJ Wason, S Dooley). *Genetic Epidemiology*, **6**, (1989), 559–569.
- [22] “Alcohol after Midazolam Sedation: Does it Really Matter?,” (JL Lichtor, J Zacny, K Korttila, JL Apfelbaum, BS Lane, G Rupani, RA Thisted, C Dohrn), *Anesthesia & Analgesia*, **72**, (1991), 661–666.
- [23] “Spreading Depression Increases Immunohistochemical Staining of Glial Fibrillary Acidic Protein,” (RP Kraig, L Dong, R Thisted, CB Jaeger). *Journal of Neuroscience*, **11**(7), (1991), 2187–2198.
- [24] “Intravenous Lidocaine does not Cause Shivering-like Tremor or Alter Thermoregulation,” (B Glosten, DI Sessler, LG Östman, EAM Faure, L Karl, RA Thisted). *Regional Anesthesia*, **16**, (1991), 218–222.
- [25] “The Automated Interview *vs.* the Personal Interview: Do Patient Responses to Preoperative Health Questions Differ?” (RE Lutner, MF Roizen, CB Stocking, RA Thisted, S Kim, PC Duke, P Pompeii, CK Cassel). *Anesthesiology*, **75**, (1991), 394–400.
- [26] “Predictors of Body Surface Area” (Y Wang, J Moss, R Thisted). *Journal of Clinical Anesthesia*, **4**, (1992), 4–10.
- [27] “Alcohol After Intravenous Midazolam-Fentanyl Sedation: Effects on Psychomotor Functioning,” (JL Lichtor, J Zacny, JL Apfelbaum, BS Lane, G Rupani, RA Thisted, C Dohrn, K Kortilla). *British Journal of Anesthesia*, **67**, (1991) 579–584.
- [28] “Sleep and Psychiatric Disorders: A Meta-Analysis,” (RM Benca, WH Obermeyer, RA Thisted, JC Gillin). *Archives of General Psychiatry*, **49**, (1992), 651–668. With editorial.
- [29] “Thromboelastogram Fails to Predict Postoperative Hemorrhage in Cardiac Patients,” (JS Wang, CY Lin, WT Hung, MF O’Connor, RA Thisted, BK Lee, RB Karp, MW Yang). *Annals of Thoracic Surgery*, **53**, (1992), 435–439.
- [31] “Central Temperature Changes are not Perceived During Epidural Anesthesia,” (B Glosten, DI Sessler, EAM Faure, L Karl, RA Thisted). *Anesthesiology*, **77**, (1992), 10–16.
- [32] “The Risk of Human Immunodeficiency Virus in Surgeons, Anesthetists, and Medical Students,” (JM Buerger, R Kim, RA Thisted, MF Roizen). *Anesthesia & Analgesia*, **75**, (1992), 118–124.
- [33] “Reassessment of Preoperative Laboratory Testing Has Changed the Test-Ordering Patterns of Physicians” (A Macario, MF Roizen, RA Thisted, S Kim, FK Orkin, C Phelps). *Surgery, Gynecology & Obstetrics*, **175**, (1992), 539–547.
- [34] “Echocardiographic Analysis of Dysfunctional and Normal Myocardial Segments Before and Immediately After Coronary Artery Bypass Graft Surgery,” (P Voci, F Bilotta, S Aronson, G Scibilia, Q Caretta, C Mercanti, B Marino, R Thisted, MF Roizen, A Reale). *Anesthesia & Analgesia*, **75**, (1992), 213–218.
- [35] “The Influence of Intravenous Albunex Injections on Pulmonary Arterial Pressure, Gas Exchange, and Left Ventricular Peak Intensity,” (R Walker, JG Weincek, S Aronson, J Zaroff, D Glock, R Thisted, SB Feinstein). *Journal of the American Society of Echocardiography*, **5**, (1992), 463–470.
- [36] “In Vitro Effects of Aprotinin on Activated Clotting Time Measured with Different Activators,” (JS Wang, CY Lin, WT Hung, RA Thisted, RB Karp). *Journal of Thoracic and Cardiovascular Surgery*, **104**, (1992), 1135–1140.
- [37] “Can Patients Use an Automated Questionnaire to Define Their Current Health Status?” (MF Roizen, D Coalson, RS Hayward, J Schmittner, RA Thisted, JL Apfelbaum, CB Stocking, P Pompei, DE Ford, *et al*). *Medical Care*, **30**, (1992), MS74–84.
- [38] “Disease-Specific Survival Following Routine Prostate Cancer Screening by Digital Rectal Examination,” (GS Gerber, IM Thompson, R Thisted, GW Chodak). *Journal of the American Medical Association*, **269**, (1993), 61–64.

- [39] “The Interaction between Alcohol and the Residual Effects of Thiopental,” (JL Lichtor, JP Zacny, DW Coalson, DC Flemming, A Uitvlugt, JL Apfelbaum, BS Lane, RA Thisted). *Anesthesiology*, **79**, (1993), 28–35.
- [40] “A proposal to use confidence intervals for visual analog scale data for pain measurement to determine clinical significance,” (S Mantha, R Thisted, J Foss, JE Ellis, MF Roizen). *Anesthesia & Analgesia*, **77**, (1993), 1041–1047.
- [41] “The initial clinical experience of 1819 physicians in maintaining anesthesia with propofol: Characteristics associated with prolonged time to awakening,” (JL Apfelbaum, TH Grasela, CC Hug, CH McLeskey, ML Nahrwold, MF Roizen, TH Stanley, RA Thisted, CA Walawander, PF White). *Anesthesia & Analgesia*, **77**, (1993), S10–14.
- [42] “The role of pharmacoepidemiology research in postmarketing surveillance and anesthesia practice/critical care medicine,” (TH Grasela, WD Watkins, CC Hug, CH McLeskey, ML Nahrwold, MF Roizen, TH Stanley, RA Thisted, CA Walawander, PF White, JL Apfelbaum). *Anesthesia & Analgesia*, **77**, (1993), S44–50.
- [43] “Hemodynamic effects of propofol: Data from over 25,000 patients,” (CC Hug, CH McLeskey, ML Nahrwold, MF Roizen, TH Stanley, RA Thisted, CA Walawander, PF White, JL Apfelbaum, TH Grasela). *Anesthesia & Analgesia*, **77**, (1993), S21–29.
- [44] “Adverse events in a multicenter Phase IV study of propofol: Evaluation by anesthesiologists and PACU nurses,” (CH McLeskey, CA Walawander, ML Nahrwold, MF Roizen, TH Stanley, RA Thisted, PF White, JL Apfelbaum, TH Grasela, CC Hug). *Anesthesia & Analgesia*, **77**, (1993), S3–9.
- [45] “Phase IV study of propofol: Validation of the data set,” (ML Nahrwold, MF Roizen, TH Stanley, RA Thisted, CA Walawander, PF White, JL Apfelbaum, TH Grasela, CC Hug, CH McLeskey). *Anesthesia & Analgesia*, **77**, (1993), S34–43.
- [46] “How do anesthesiologists select patients when introducing a new drug into practice?” (MF Roizen, TH Stanley, RA Thisted, CA Walawander, PF White, JL Apfelbaum, TH Grasela, CC Hug, CH McLeskey, ML Nahrwold). *Anesthesia & Analgesia*, **77**, (1993), S30–33.
- [47] “Effects on recovery when isoflurane is used to supplement propofol-nitrous oxide anesthesia,” (PF White, TH Stanley, JL Apfelbaum, TH Grasela, CC Hug, CH McLeskey, ML Nahrwold, MF Roizen, RA Thisted, CA Walawander). *Anesthesia & Analgesia*, **77**, (1993), S15–20.
- [48] “Predictive and Diagnostic Tests of Renal Failure: A Review,” (M Kellen, S Aronson, MF Roizen, J Barnard, RA Thisted). *Anesthesia & Analgesia*, **78**, (1994), 134–142.
- [49] “Association of Preoperative Risk Factors with Postoperative Acute Renal Failure,” (BK Novis, MF Roizen, S Aronson, RA Thisted). *Anesthesia & Analgesia*, **78**, (1994), 143–149.
- [50] “Results of Conservative Management of Clinically Localized Prostate Cancer,” (GW Chodak, RA Thisted, GS Gerber, J-E Johansson, J Adolfsson, G Jones, G Chisholm, B Moskovitz, J Warner). *New England Journal of Medicine*, **330**, (1994), 242–248.
- [51] “Relative Effectiveness of Four Preoperative Tests for Predicting Adverse Cardiac Outcomes After Vascular Surgery: A Meta-Analysis,” (S Mantha, MF Roizen, J Barnard, RA Thisted, JE Ellis, J Foss). *Anesthesia & Analgesia*, **79**, (1994), 422–433.
- [52] “Premedication with Oral and Transdermal Clonidine Provides Safe and Efficacious Postoperative Sympatholysis,” (JE Ellis, G Drijvers, S Pedlow, SP Laff, MJ Sorrentino, JF Foss, M Shah, JR Busse, S Mantha, J McKinsey, J Osinski, RA Thisted, MF Roizen). *Anesthesia & Analgesia*, **79**, (1994), 1133–40.
- [53] “Mucosal allergy in the absence of systemic allergy in nasal polyposis and rhinitis: a meta-analysis,” (JS Shatkin, KG Delsupehe, RA Thisted, JP Corey). *Otolaryngology – Head & Neck Surgery*, **111**(5), (1994), 553–6.
- [54] “Estimation of the association between desipramine and the risk for sudden death in 5 to 14-year-old children,” (J Biederman, RA Thisted, L Greenhill, ND Ryan). *Journal of Clinical Psychiatry*, **56**, (1995), 87–93.
- [55] “A comparison of intraarticular morphine to bupivacaine for pain control following local knee arthroscopy in the day surgery setting: A prospective, randomized, double-blinded study,” (JW

- Jaureguito, JF Wilcox, SJ Cohn, RA Thisted, B Reider). *American Journal of Sports Medicine*, **23**, (1995), 350–3.
- [56] “Prospective, randomized, double-blind trial of BQ-123 and bosentan for prevention of vasospasm following subarachnoid hemorrhage in monkeys.” (A Hino, BK Weir, RL Macdonald, RA Thisted, et al) *Journal of Neurosurgery*, **83**, (1995), 503–9.
- [57] “Resolved: cardiac arrhythmias make desipramine an unacceptable choice in children.” (JS Werry, J Biederman, R Thisted, L Greenhill, et al) *Journal of the American Academy of Child & Adolescent Psychiatry*, **34**, (1995), 1239–45; discussion 1245–8.
- [58] “Short-term outcomes after cryosurgical ablation of the prostate in men with recurrent prostate carcinoma following radiation therapy,” (GT Bales, MJ Williams, M Sinner, RA Thisted, GW Chodak), *Urology*, **46**(5), (1995), 676–80.
- [59] “Results of radical prostatectomy in men with clinically localized prostate cancer,” (GS Gerber, RA Thisted, PT Scardino, HG Frohmuller, FH Schroeder, DF Paulson, AW Middleton, Jr., DB Rukstalis, JA Smith, Jr., PF Schellhammer, M Ohori, GW Chodak), *JAMA*, **276**(8), (1996), 615–9.
- [60] “Eye injuries after nonocular surgery. A study of 60,965 anesthetics from 1988 to 1992,” (S Roth, RA Thisted, JP Erickson, S Black, BD Schreider), *Anesthesiology*, **85**(5), (1996), 1020–7.
- [61] “Glutamine protects intestinal epithelial cells: Role of inducible HSP70,” (PE Wischmeyer, MW Musch, MB Madonna, R Thisted, EB Chang), *Am J Physiol*, **272** (*Gastrointest Liver Physiol*, **35**), 1997, G879–G884.
- [62] “Postcesarean analgesia with both epidural morphine and intravenous patient-controlled analgesia: Neurobehavioral outcomes among nursing neonates.” (B Wittels, B Glosten, EAM Faure, AH Moawad, M Ismail, J Hibbard, JA Senal, SM Cox, SC Blackman, L Karl, RA Thisted) *Anesthesia & Analgesia*, **85** (1997) 600–606.
- [63] “Results of radical prostatectomy in men with locally advanced prostate cancer: multi-institutional pooled analysis.” (Gerber GS, Thisted RA, Chodak GW, Schroder FH, Frohmuller HG, Scardino PT, Paulson DF, Middleton AW Jr, Rukstalis DB, Smith JA Jr, Ohori M, Theiss M, Schellhammer PF) *European Urology*. **32**(4), (1997) 385–390.
- [64] “SPECT brain imaging in epilepsy: a meta-analysis.” (Devous MD Sr, Thisted RA, Morgan GF, Leroy RF, Rowe CC) *Journal of Nuclear Medicine*, **39**(2), (1998) 285–293.
- [65] “Computer Architecture,” *Encyclopedia of Biostatistics*, Wiley: New York. (1998).
- [66] “Is geographic variation in hip fracture rates related to current or former state of residence?” (DS Lauderdale, RA Thisted, J Goldberg) *Epidemiology*, **9**(5), (1998) 574–577.
- [67] “Tryptase levels are not increased during vancomycin-induced anaphylactoid reactions” (CL Renz, D Laroche, JD Thurn, HA Finn, JP Lynch, R Thisted, J Moss) *Anesthesiology*, **89**, (1998) 620–625.
- [68] “Clinical trials in general surgical journals: are methods better reported?” (LP Schumm, JS Fisher, RA Thisted, J Olak) *Surgery*, **125**(1), (1999) 41–45.
- [69] “Comparing methods of clinical measurement: Reporting standards for Bland and Altman analysis” (S Mantha, MF Roizen, LA Fleischer, R Thisted, J Foss) *Anesthesia & Analgesia*, **90** (2000) 593–602.
- [70] “New scoring system identifies kidney outcome with radiation therapy in acute renal allograft rejection” (Chen LM, Godinez J, Thisted RA, Woodle ES, Thistlewaite JR, Powers C, Haraf D) *Int J Radiat Oncol Biol Phys*, **46**(4) (2000) 999–1003.
- [71] “A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis” (Cohen RD, Woseth DM, Thisted RA, Hanauer SB) *Am J Gastroenterol*, **95**(5) (2000) 1263–76.
- [72] “The impact of contralateral breast cancer on the outcome of breast cancer patients treated with mastectomy,” (I Abdalla, R Thisted, R Heimann) *Cancer J Sci Am*, **6**(4) (2000) 266–72.
- [73] “SPECT perfusion imaging in the diagnosis of Alzheimer’s disease: A clinical-pathologic study,” (W Jagust, R Thisted, MD Devous, Sr., R Van Heertum, H Mayberg, K Jobst, AD Smith, N Borys), *Neurology*, **56**(7), (2001), 950–6.

- [74] “Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: A multicenter, randomized, placebo-controlled trial,” (SL Sacks, RA Thisted, TM Jones, RA Barbarash, DJ Mikolich, GE Ruoff, JL Jorizzo, LB Gunnill, DH Katz, MH Khalil, PR Morrow, GJ Yakatan, LE Pope, JE Berg), *J Am Acad Dermatol*, **45**(2), (2001), 222–30.
- [75] “BIS monitoring to prevent awareness during general anesthesia,” (MF O’Connor, SM Daves, A Tung, RI Cook, R Thisted, J Apfelbaum), *Anesthesiology*, **94**(3), (2001), 520–2.
- [76] “Impact of Interpreter Services on Delivery of Health Care to Limited-English-proficient Patients,” (E Jacobs, DS Lauderdale, D Meltzer, J Shorey, W Levinson R Thisted) *JGIM*, **16** (2001) 468–74.
- [77] “Bone mineral density and fracture among prevalent kidney stone cases in the Third National Health and Nutrition Examination Survey,” (DS Lauderdale, RA Thisted, M Wen, MJ Favus), *Journal of Bone Mineral Research*, **16**(10), (2001), 1893–8.
- [78] “The effects of morphine on human articular cartilage of the knee: an in vitro study,” (JW Jaureguito, JF Wilcox, RA Thisted, C Phillips, B Cunningham, B Reider), *Arthroscopy*, **18**(6), (2002), 631–6.
- [79] “Are There Social Determinants of Health?” (RA Thisted), *Perspectives in Biology and Medicine*, **46**(3 Suppl), (2003 Summer), S65–S73.
- [80] “Exercise Capacity and the Risk of Death in Women: The St James Women Take Heart Project,” (M Gulati, DK Pandey, MF Arnsdorf, DS Lauderdale, RA Thisted, RH Wicklund, AJ Al-Hani, HR Black), *Circulation* **108**(13), (2003), 1554–9.
- [81] “Causes and Consequences of Kidney Loss in Patients with Nephrolithiasis,” (E Worcester, JH Parks, MA Josephson, RA Thisted, FL Coe), *Kidney International*, **64**(6), (2003), 2204–13.
- [82] “Postoperative Maintenance of Crohns Disease Remission With 6-Mercaptopurine, Mesalamine, or Placebo: A 2-Year Trial,” (SB Hanauer, BI Korelitz, P Rutgeerts, MA Peppercorn, RA Thisted, RD Cohen, DH Present). *Gastroenterology*, **127**, (2004), 723–729.
- [83] “Treatment of Pseudobulbar Affect in ALS with Dextromethorphan/Quinidine: A Randomized Trial,” (BR Brooks, RA Thisted, SH Appel, WG Bradley, RK Olney, JE Berg, LE Pope, RA Smith), *Neurology*, **63**, (2004), 1364–1370.
- [84] “Measuring Pseudobulbar Affect in ALS,” (RA Smith, JE Berg, LE Pope, RA Thisted), *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders*, Sep;5 Suppl 1: (2004) 99–102.
- [85] “Validation of the CNS Emotional Lability Scale for pseudobulbar affect (pathological laughing and crying) in multiple sclerosis patients,” (RA Smith, JE Berg, LE Pope, JD Callahan, D Wynn, RA Thisted), *Multiple Sclerosis*, **10**, (2004), 679–685.
- [86] “The Effect of Physician Disclosure of Financial Incentives on Trust,” (W Levinson, A Kao, AM Kuby, RA Thisted), *Archives of Internal Medicine*, **165**(6): 625–630, (2005).
- [87] “Distinct temporal phases in the behavioral pharmacology of LSD: dopamine D<sub>2</sub> receptor-mediated effects in the rat and implications for psychosis,” (D Marona-Lewicka, RA Thisted, DE Nichols), *Psychopharmacology* (Berl), **180**: 427–435, (2005).
- [88] “The Prognostic Value of a Nomogram for Exercise Capacity in Women,” (M Gulati, HR Black, LJ Shaw, MF Arnsdorf, CNB Merz, MS Lauer, TH Marwick, DK Pandey, RH Wicklund, RA Thisted), *New England Journal of Medicine*, **353**(5): 468–475, (2005).
- [89] “Prognostic Value of the Duke Treadmill Score in Asymptomatic Women,” (M Gulati, MF Arnsdorf, LJ Shaw, DK Pandey, RA Thisted, D Lauderdale, R Wicklund, AJ Al-Hani, HR Black), *American Journal of Cardiology*, **96**: 369–375, (2005).
- [90] “Not All Patients Want to Participate in Decision-Making. A National Study of Public Preferences,” (W Levinson, A Kao, A Kuby, RA Thisted), *Journal of General Internal Medicine*, **20**(6): 531–535, (2005).
- [91] “Breastfeeding history and overweight in Latino preschoolers,” (M Kersey, R Lipton, M Sanchez-Rosado, J Kumar, R Thisted, J Lantos), *Ambulatory Pediatrics*, **5**(6): 355–358, (2005).
- [92] “Randomized Controlled Trial of Dextromethorphan/Quinidine for Pseudobulbar Affect in Multiple Sclerosis,” (H Panitch, R Thisted, R Smith, L Pope, J Berg), *Annals of Neurology*, **59**: 780–787, (2006).

- [93] “Loneliness as a specific risk factor for depressive symptoms in older adults: Cross-sectional and longitudinal analyses,” (JT Cacioppo, ME Hughes, LJ Waite, LC Hawkley, R Thisted), *Psychology and Aging*, **21(1)**: 140–151, (2006).
- [94] “Dextromethorphan and Quinidine in Adult Patients With Uncontrolled Painful Diabetic Peripheral Neuropathy: A 29-Day, Multicenter, Open-Label, Dose-Escalation Study,” (RA Thisted, L Klaff, SL Schwartz, JP Wymer, NW Culligan, G Gerard, LE Pope, JE Berg), *Clinical Therapeutics*, **28**: 1607–1618, (2006).
- [95] “From social structural factors to perceptions of relationship quality and loneliness: The Chicago Health, Aging, and Social Relations Study,” (LC Hawkley, ME Hughes, LJ Waite, CM Masi, RA Thisted, JT Cacioppo), *J Gerontol B Psychol Sci Soc Sci.*, **63(6)**: S375–S384, (2008). [PMCID: PMC2769562.]
- [96] “Loneliness predicts reduced physical activity: Cross-sectional & longitudinal analyses,” (LC Hawkley, RA Thisted, JT Cacioppo), *Health Psychology*, **28(3)**: 354–63, (2009).[PMCID: PMC2791498.]
- [97] “VLDL best predicts aortic root atherosclerosis in LDL receptor deficient mice,” (PA Vanderlaan, CA Reardon, RA Thisted, GS Getz), *J Lipid Res.*, **50(3)**: 376–85, (2009). [PMCID: PMC2638101.]
- [98] “Perceived social isolation makes me sad: 5-year cross-lagged analyses of loneliness and depressive symptomatology in the Chicago Health, Aging, and Social Relations Study,” (JT Cacioppo, LC Hawkley, RA Thisted), *Psychology and Aging*, **25(2)**: 453–63, (2010). [PMCID: PMC2922929.]
- [99] “Loneliness predicts increased blood pressure: Five-year cross-lagged analyses in middle-aged and older adults,” (LC Hawkley, RA Thisted, CM Masi, JT Cacioppo), *Psychology and Aging*, **25(1)**: 132–141, (2010). [PMCID: PMC2841310.]
- [100] “The absorption hypothesis: learning to hear God in evangelical Christianity,” (TM Luhrmann, H Nusbaum, R Thisted), *American Anthropologist*, **112(1)**: 66–78, (2010).
- [101] “Heart Rate Response to Exercise Stress Testing in Asymptomatic Women: The St. James Women Take Heart Project,” (M Gulati, LJ Shaw, RA Thisted, HR Black, CN Bairey Merz, MF Arnsdorf), *Circulation*, **122**: 130–137, (2010).
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### Computer Software and Data Bases

- [S1] *The Literary Detective* (SA Kurtz, RA Thisted). Version 0.14. Computer software for Macintosh computers. The University of Chicago: Chicago, Illinois. 1989.
- [S2] *Current Index to Statistics/Extended Database, 1993 Edition*. (BE Trumbo, RA Thisted, Eds). Bibliographic database of the statistical literature on CD-ROM. American Statistical Association and Institute of Mathematical Statistics. 1993.
- [S3] *Current Index to Statistics/Extended Database, 1994 Edition*. (RA Thisted, Editor; B Trumbo, M Wichura, Eds). CD-ROM. American Statistical Association and Institute of Mathematical Statistics. 1994.
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- [S6] *Current Index to Statistics/Extended Database, 1997 Edition*. (Michael Wichura, Ronald Thisted, Klaus Hinkelmann, Eds). CD-ROM. American Statistical Association and Institute of Mathematical Statistics. 1997.

- [S7] *Current Index to Statistics/Extended Database, Release 7.* (Michael Wichura, Ronald Thisted, Klaus Hinkelmann, Eds). *CD-ROM*. American Statistical Association and Institute of Mathematical Statistics. 1998.
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#### Book Chapters, Comments, Reviews, and Other Publications

- [M1] Comment on “A Simulation Study of Alternatives to Ordinary Least Squares,” by Dempster, Schatzoff, and Wermuth, *Journal of the American Statistical Association*, **72**, (1977), 77–106.
- [M2] *Operations Research: Principles and Practice*, by Phillips, Ravindran, and Solbert. (Book Review) *Journal of the American Statistical Association*, **72**, (1977), 692–693.
- [M3] *Statistical Methods for Digital Computers*, by Enslein, Ralston, and Wilf. (Book review) *Computing Reviews*, **20**, (1979), 309–312.
- [M4] Comment on “A Critique of Some Ridge Regression Methods,” by Smith and Campbell, *Journal of the American Statistical Association*, **75**, (1980), 81–86.
- [M5] “The Effect of Personal Computers on Statistical Practice”. *Computer Science and Statistics: Thirteenth Symposium on the Interface*, W. F. Eddy, ed. (1981), 25–30.
- [M6] “Decision-Theoretic Regression Diagnostics.” *Statistical Decision Theory and Related Topics III*, **2** (1982), S. S. Gupta and J. Berger, eds. Academic Press: New York, 363–382.
- [M7] “A Remark on AS 127: Generation of Random Orthogonal Matrices” (M Tanner, R Thisted). *Applied Statistics*, **31**, (1982), 190–192.
- [M8] “Treatment of Depression,” (Letter) *Journal of the American Medical Association*, **249:18**, (1983), 2457–2458.
- [M9] “An Appraisal of Statistical Graphics,” in *Statistics: An Appraisal*, H. A. David and H. T. David, eds., Iowa State University Press, (1984), 605–624.
- [M10] *Statistical Software: A Comparative Review*, by Ivor Francis. (Book Review) *SIAM Review*, **26**, (1984), 294–297.
- [M11] “Hacking Away at Morality,” (Letter) *Communications of the ACM*, **27**, (1984), 8. [“Privacy” should read “piracy.” Editorial correction, **27**, (1984), 176.]
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- [M13] “Knowledge Representation For Expert Data Analysis Systems,” in *Computer Science and Statistics: 17th Symposium on the Interface*, DM Allen, ed. North-Holland (1986), 43–48.
- [M14] “Representing Statistical Knowledge and Search Strategies for Expert Data Analysis Systems,” Chapter 11 in *Artificial Intelligence and Statistics*, William A. Gale, editor. (1986) Addison-Wesley: Reading, Massachusetts. 267–284.
- [M15] “Tools for Data Analysis Management,” in *Computer Science and Statistics: Eighteenth Symposium on the Interface*, Thomas Boardman, Editor. (1986) American Statistical Association: Washington, 152–159.
- [M16] “Sources of Error in Graphical Perception: A Critique and an Experiment” (M Morris, R Thisted). *Proceedings of the Section on Statistical Graphics*. (1986). American Statistical Association: Washington, 43–48.
- [M17] *Elements of Graphing Data*, by William S. Cleveland. (Book review) *Computing Reviews*, (1986), 179–180.
- [M18] Comment on “Collinearity and least squares regression,” by G. W. Stewart, *Statistical Science* **2**, (1987), 91–93.
- [M19] *Statistical Image Processing and Graphics*, Edward J. Wegman and Douglas J. DePriest, editors. (Book review) *Technometrics* **30**, (1988), 126–127.

- [M20] *Graphical Exploratory Data Analysis*, by S. H. C. du Toit, A. G. W. Steyn, and R. H. Stumpf. (Book review) *Journal of the American Statistical Association*, **84**, (1989), 614.
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- [M22] *Linear Least Squares Computations*, by R. W. Farebrother. (Book review) *Technometrics*, **33**, (1991), 368–369.
- [M23] “Complications of Patients Undergoing Lumbar Discectomy in Community Hospitals,” (L Ramirez, R Thisted). chapter in *Complications of Spinal Surgery*, Edward Tarlov, ed., American Association of Neurological Surgeons: Park Ridge, (1991).
- [M24] “Computers and Modern Statistics,” (RA Thisted, PF Velleman). Chapter 3 in *Perspectives on Contemporary Statistics*, David Hoaglin and David F. Moore, eds. Mathematical Association of America: Washington. (1992).
- [M25] “Interdisciplinary Statistics Education.” In *Modern Interdisciplinary University Statistics Education: Proceedings of a Symposium*, Committee on Applied and Theoretical Statistics, National Research Council (1994), 110–116.
- [M26] *Artificial Intelligence Frontiers in Statistics*, D. J. Hand, editor. (Book review) *Journal of the American Statistical Association*, **89**, (1994), 719–720.
- [M27] “Incidence of postdural puncture headache in morbidly obese parturients [letter],” (E Faure, R Moreno, R Thisted). *Regional Anesthesia*, **19**(5), (1994), 361–363.
- [M28] “On ‘Smoking is not a predictor of mortality and morbidity following coronary artery bypass grafting’ by JR Utley, et al.” (Invited Commentary) (J Olak, R Thisted) *Journal of Cardiac Surgery*, **11**, (1996) 385–6.
- [M29] “Re: Long-term survival and mortality in prostate cancer treated with noncurative intent [letter; comment],” (GW Chodak, RA Thisted), *Journal of Urology*, **155**(6), (1996), 2039; discussion 2039–41.
- [M30] Comment on “The Gaussian Hare and the Laplacian Tortoise: Computability of Squared-Error versus Absolute-Error Estimators,” by Stephen Portnoy and Roger Koenker, *Statistical Science*, **12**, (1997), 296–298.
- [M31] “6-Mercaptopurine and Mesalamine for prevention of relapse after conservative surgery for Crohn’s Disease,” [Reply to Letter] (SB Hanauer, R Cohen, RA Thisted, P Rutgeerts, DH Present, BI Korelitz), *Gastroenterology*, **128**(1), (2005), 249–251.
- [M32] “Treatment of Crohn’s disease: the ‘Long’ of it,” [Editorial] (SB Hanauer, RA Thisted), *Gastroenterology*, **128**(7), (2005), 2164–6.
- [M33] “Baseline Adjustment: Issues for Mixed-Effect Regression Models in Clinical Trials,” *ASA Proceedings of the Joint Statistical Meetings*, 386–391. American Statistical Association (Alexandria, VA). (2006).
- [M34] “Happiness and the invisible threads of social connection: The Chicago Health, Aging, and Social Relations Study.” (JT Cacioppo, LC Hawkey, A Kalil, ME Hughes, L Waite, RA Thisted). Chapter 10 in *The Science of Subjective Well-Being*, Michael Eid and Randy J. Larsen, eds. Guilford Press: New York. (2008), 195–219.
- [M35] “Multilevel investigations: Conceptual mappings and perspectives.” (JT Cacioppo, GG Berntson, RA Thisted). Chapter 17 in *Biosocial Surveys*, Committee on Advances in Collecting and Utilizing Biological Indicators and Genetic Information in Social Science Surveys. M Wienstein, JW Vaupel, and KW Wachter, eds. The National Academy Press: Washington, DC (2008), 367–380.
- [M36] “Epilogue.” Chapter 16 in *Invisible Forces and Powerful Beliefs: Gravity, Gods, and Minds*, The Chicago Social Brain Network. FT Press Science: Upper Saddle River, NJ. (2010) 197–205.

### Selected Grants and Contracts

R01 HD069500 Lauderdale, D (PI) 7/1/2011–8/31/2014 (NIH/NIA)  
*Social Relationships, Economic Shocks, Sleep and Wellbeing Among Older Adults*  
 Role: Co-Investigator, Biostatistician

P30 CA14599 Le Beau, M. (PI) 05/1/08–03/31/18 (NIH/NCI)  
*UCCRC-Cancer Center Support Grant; Subproject: Biostatistics Facility*  
 Role: Scientific Director of Biostatistics

UL1 TR000430 Solway, J. (PI) 9/17/07–05/31/17 (NIH)  
*Clinical and Translational Science Award*  
 Roles: Population Sciences Cluster Director, Clinical Research Training Program Co-Director

U01 DK62429 Cho, J (PI) 9/30/02–8/31/21 (NIH/NIDDK)  
*IBD Genetics Consortium Data Coordinating Center*  
 Role: Director, Data Management Core (Site PI)

HHS 290-2007-10058 Meltzer, D (PI) 10/26/09–10/25/12 (AHRQ/ARRA/BCBS)  
*American Recovery and Reinvestment Act of 2009: Comprehensive EPC Comparative Effectiveness Reviews for Effective Health Care*  
 Role: Statistical consultant

R34 AI080962 Solway, J (PI) 9/4/08–8/31/09 (NIH/NIAID)  
*Evaluation of Lovastatin in Severe Persistent Asthma (ELiSPA)*  
 Role: Co-Investigator, Biostatistician

5K30 HL04093-02 Coe, F. (PI) 6/1/99–9/27/07 (NIH)  
*Clinical Research Training Program*  
 Roles: Program Co-Director, Seminar Director

P01 AG18911 Cacioppo, J. (PI) 7/1/01–6/30/06 (NIH)  
*Social Isolation, Health and the Aging Process; Biostatistical Core B*  
 Role: Director, Biostatistics Core

R01 CA92443-01 Meltzer, D. (PI) 9/1/01–8/31/04 (NIH)  
*Cost-Effectiveness of Prostate Cancer Screen/Treatment*  
 Role: Advisory Panel

R01 HS09982 Thisted, R. (PI) 9/15/99–8/31/03 (AHRQ)  
*Patient Preferences for Disclosure: A National Survey*  
 Role: Principal Investigator (*vice* Levinson), Statistician

R01 NS40229 Frank (PI) 9/18/99–6/30/03 (NIH)  
*Hemicraniectomy for Swelling from Cerebral Infarction*  
 Role: Director, Data Coordinating Center

Cassell, C. (PI) 7/1/93–6/30/95  
 Thisted, R. (PI) 7/1/95–6/30/98  
 Levinson, W. (PI) 7/1/98–6/30/01  
 Lantos, J. (PI) 7/1/02–6/30/06 (Robert Wood Johnson Foundation)  
*Clinical Scholars Program*  
 Role: Co-PI to 1998, Co-Director to 1999; Core-Faculty; Advisory Board

## Teaching

### Recent Courses Taught

- 2014 Health Studies 310: Epidemiologic Methods
  - Health Studies 333: Longitudinal Data Analysis
  - Health Studies 307: Clinical Epidemiology (Lecture: Meta-Analysis)
  - Essentials of Patient-Oriented Research (Lecture: Study Design)
- 2013 Health Studies 307: Clinical Epidemiology (Lecture: Experimental Study Design)
  - Essentials of Patient-Oriented Research (Lecture: Study Design)
  - Health Studies 333: Longitudinal Data Analysis
- 2012 Health Studies 307: Clinical Epidemiology
  - Health Studies 333: Longitudinal Data Analysis
  - Seminar in Clinical Research Methods (20 weeks)
  - Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)
- 2011 Health Studies 329: Introduction to Clinical Trials
  - Health Studies 333: Longitudinal Data Analysis
  - Seminar in Clinical Research Methods (30 weeks)
  - Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)
- 2010 Health Studies 327: Biostatistical Methods
  - Health Studies 333: Longitudinal Data Analysis
  - Seminar in Clinical Research Methods (30 weeks)
  - Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)
- 2009 Health Studies 327: Biostatistical Methods
  - Seminar in Clinical Research Methods (30 weeks)
  - Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)
  - Family Medicine 304: Epidemiology and Clinical Investigation (Lecture: Screening Tests)
- 2008 Health Studies 327: Biostatistical Methods
  - Seminar in Clinical Research Methods (30 weeks)
  - Statistics 307/Computer Science 378: Numerical Computation
- 2007 Health Studies 327: Biostatistical Methods
  - Seminar in Clinical Research Methods (30 weeks)
  - Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)
  - Statistics 307/Computer Science 378: Numerical Computation
- 2006 Health Studies 327: Biostatistical Methods
  - Seminar in Clinical Research Methods (30 weeks)
  - Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)
- 2005 Statistics 307: Numerical Computation
  - Seminar in Clinical Research Methods (30 weeks)
- 2004 Health Studies 327: Biostatistical Methods
  - Health Studies 541: Epidemiology and Clinical Investigation (Lecture: Chronic Disease Epidemiology)
  - Medicine 777: Advanced Clinical Pharmacology (Lecture: Pharmacoepidemiology)
  - Medicine 603: Critical Appraisal of Medical Literature (Lecture: Statistical issues)
  - Seminar in Clinical Research Methods (30 weeks)
- 2003 Health Studies 541: Epidemiology and Clinical Investigation
  - Health Studies 327: Biostatistical Methods
  - Medicine 777: Advanced Clinical Pharmacology (Lecture on Pharmacoepidemiology)

- Medicine 603: Critical Appraisal of Medical Literature (Lecture: Statistical issues)  
Seminar in Clinical Research Methods (30 weeks)
- 2002 Health Studies 541: Epidemiology and Clinical Investigation  
Medicine 777: Advanced Clinical Pharmacology (Lecture on Pharmacoepidemiology)  
Medicine 603: Critical Appraisal of Medical Literature (Lecture: Statistical issues)  
Seminar in Clinical Research Methods (30 weeks)
- 2001 Health Studies 541: Epidemiology and Clinical Investigation  
Statistics 224: Applied Regression Analysis  
Medicine 777: Advanced Clinical Pharmacology (Lecture on Pharmacoepidemiology)  
Medicine 603: Critical Appraisal of Medical Literature (Lecture: Statistical issues)  
Seminar in Clinical Research Methods (30 weeks)
- 2000 Health Studies 541: Epidemiology and Clinical Investigation  
Statistics 224: Applied Regression Analysis  
Medicine 777: Advanced Clinical Pharmacology (Lecture on Pharmacoepidemiology)  
Seminar in Clinical Research Methods (30 weeks)
- 1999 Statistics 307: Numerical Computation  
Statistics 226: Categorical Data Analysis  
Seminar in Clinical Research Methods (15 weeks)

#### **Refereeing, 2005–**

*Annals of Statistics*  
*Annals of Applied Statistics*  
*Regulatory Pharmacology and Toxicology*  
*JAMA Oncology*  
*JAMA Psychiatry*  
*Journal of Clinical Oncology*  
*Journal of Surgical Research*  
*Neuropsychopharmacology*  
*Perspectives in Biology and Medicine*  
*PLoS ONE*  
*Statistics in Medicine*  
NIH, Center for Scientific Review (Surgery, Anesthesiology and Trauma study section)  
NIH, Center for Scientific Review (Challenge Grant Editorial Panel HDM-P)  
NSF, Division of Mathematical Sciences  
Research Grants Council of Hong Kong

## University Committees

### Current appointments:

Emeriti Faculty Steering Committee, 2019–.  
University Benefits Committee, 2019–.

### Previous appointments (since 1982):

Working Group on Innovation, Transparency, Conflict of Interest, 2015–2018.  
Compliance Committee, 2014–2018.  
Standing Committee on Academic Fraud, 2014–2018.  
Standing Committee on Individual Conflict of Interest 2015–2018.  
Steering Committee, Spring 2016 Climate Survey on Diversity and Inclusion, 2015–2016.  
*ad hoc* Committee for the Spring 2015 Climate Survey on Sexual Misconduct, 2015.  
Executive Committee, Center for Cognitive and Social Neuroscience, 2007–2015.  
Executive Committee, Institute of Translational Medicine (CTSA), 2007–2015.  
Committee on Appointments and Promotions, Biological Sciences Division, 2014.  
Data Stewardship Committee, University of Chicago Medicine, 2013–2014.  
Health Professions Faculty Advisory Committee, 2013–2014.  
Center for Research Informatics Oversight Committee, 2011–2014.  
Research Advisory Committee, University of Chicago Medicine, 2010–2014.  
Research Planning Review Committee, University of Chicago Medicine, 2012–2013.  
Committee of Basic Science Chairs, Biological Sciences Division, 1999–2012.  
Executive Committee, Clinical Research Training Program, 1999–2012.  
University of Chicago Medical Center, Budget Oversight Committee, 2007–2010.  
Executive Committee, Division of Biological Sciences, 2000–2009.  
*ad hoc* Faculty Science Review Committee, 2009.  
Committee of Clinical Chairs, Biological Sciences Division, 1999–2006.  
Advisory Committee, Robert Wood Johnson Clinical Scholars Program, 1999–2006.  
Executive Committee, University of Chicago Cancer Research Center, 2000–2005.  
Search Committee (Chair), Chairman of Department of Psychiatry, 2003–2004.  
Committee to Review Appointment and Promotion Criteria (BSD), 2003–2004.  
Tenure and Tracks Committee (BSD), 2003–2004.  
Committee to Advise the Provost on Federal Wide Assurance (Chair), 2003.  
Research Aims Committee, Division of Biological Sciences, 2002–2003.  
Search Committee, Chairman of Department of Obstetrics & Gynecology, 2000–2003.  
Committee to Advise the President on the Dean of the Biological Sciences Division, 2001–2002.  
Search Committee (Chair), Chairman of Department of Family Medicine, 2000–2002.  
Provost's Committee on Medical Informatics, 2000–2001.  
Clinical Translational Advisory Group, Biological Sciences Division, 1999–2001.  
Co-chair, Committee on Law and Medicine, BSD and Law School, 1999–2000.  
Working Group on Clinical Data Sharing, 1999–2001.  
Executive Committee, Department of Anesthesia & Critical Care, 1994–1998.  
Institutional Review Board, Division of Biological Sciences, 1983–1986, 1987–1997.  
Faculty Campus Planning Committee, 1993–1996.  
College Curriculum Committee, 1990–1996.  
Board of Computing Activities and Services 1981–1986, 1991–1994.  
Physical Sciences Division, Space/Facilities Committee, 1992–1994.  
Committee on Family Practice (BSD), 1993.  
Provost's Committee on Health Studies, 1993.

Health Studies Committee (BSD), 1991–1992.  
College Council, 1979–1982, 1983–1986, 1989–1992.

# EXHIBIT B

- 1) My full name is Ronald Aaron Thisted. I reside at 5729 South Woodlawn Avenue, Chicago, Illinois 60637 USA.
- 2) Since December 2018, I have been self employed as a statistical consultant, and have also served part time as Professor Emeritus at the University of Chicago.
- 3) Since January 2020 I have provided deposition, cross-examination, and/or trial testimony as an expert witness in the following cases:
  - a) *Bayer Inc. and Bayer Intellectual Property GMBH v. Teva Canada Limited and Apotex Inc.*, Federal Court of Canada Court Files T-1960-18 and T-2093-18,
  - b) *Biodelivery Sciences International, Inc., and Arius Two, Inc.*, v. Alvogen PB Research & Development LLC, Alvogen Malta Operations Ltd., Alvogen Pine Brook LLC, Alvogen, Inc., and Alvogen Group, Inc. C. A. No. 1:18-1395-CFC; and *Biodelivery Sciences International, Inc., and Arius Two, Inc.*, v. Chemo Research, S.L., Intelgenx Corp., and Intelgenx Technologies Corp., C. A. No. 1:19-cv-00444-CFC, (District of Delaware),
  - c) *AstraZeneca AB v. Zydus Pharmaceuticals (USA) Inc.*, 1:18-cv-00664-RGA (D. Del.),
  - d) *Allergan Sales, LLC et al. v. Sandoz, Inc. et al.*, 2:17-cv-10129-CCC-MF (D. New Jersey),
  - e) *Amgen Inc. v. Sandoz Inc.*, C.A. No. 18-11026(MAS)(DEA) (D. NJ),
  - f) *Craig Couturier v. C. R. Bard, Inc, et al.*, 2:19-cv-12497-ILRL-DPC (E. Dist. Louisiana),
  - g) *Astellas Pharma Inc., et al.*, v. Sandoz Inc., et al., 1:20-cv-01589-JFB-CJB (D. Del.),
  - h) *Neuraxpharm Sweden AB v Biogen MA Inc.*, Case number PMT 11833-22, filed on 12 August 2022; *Sandoz A/S v Biogen MA Inc.*, Case number PMT 387-23, filed on 10 January 2023; and *Viatrix AB v Biogen MA Inc.*, Case number PMT 402-23, filed on 10 January 2023; all in the Patent and Market Court, Stockholm, Sweden.

Party on behalf of whom testimony was offered is in *italics* above.

Ronald A. Thisted, PhD  
12 January 2025

# EXHIBIT C

## MATERIALS CONSIDERED

Patent Documents
U.S. Patent No. 11,826,327 (UTC PH-ILD 005310)
U.S. Patent No. 10,716,793 (UTC PH-ILD 009772)
U.S. Provisional Patent Application No. 63/011,810 (UTC PH-ILD 069472)
U.S. Provisional Patent Application No. 63/160,611
Expert Reports
Redacted Version of 2024-12-20 Expert Report of Dr. Richard Channick
2024-12-20 Expert Report of Dr. Nicholas Hill
2024-03-04 D.I. 035 Redacted Version of 2024-02-26 D.I. 28 Declaration of Steven D. Nathan, M.D.
Litigation Materials
Redacted Version of D.I. 123, Joint Claim Construction Brief (D.I. 127)
Claim Construction Order (D.I. 155)
Excerpt of 2024-11-12 Chunqin Deng Deposition Transcript
Ex. 23 from 2024-09-05 D.I. 128 (Redacted Version of D.I. 124 Appendix)
2024-04-19 (D.I. 070) Redacted Version of Declaration of R. Channick (D.I. 54)
Regulations
21 C.F.R. 314.126
Literature
M. Agarwal & A.B. Waxman, <i>Inhaled Treprostinil in Group-3 Pulmonary Hypertension</i> , 34 J. Heart Lung Transplant S343 (2015) (UTC PH-ILD 009828)
Adrian G Barnett et al., <i>Regression to the Mean: What It Is and How To Deal With It</i> , 34 Int'l J. Epidemiology 215 (2005)
Debra S. Echt et al., <i>Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo</i> , 324 N. Eng. J. Med. 781 (1991)
Mariana Faria-Urbina et al., <i>Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease</i> , 196(2) Lung 139 (2018) (UTC PH-ILD 009936)
Supplementary Material for Mariana Faria-Urbina et al., <i>Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease</i> , 196(2) Lung 139 (2018)
Press Release, United Therapeutics Announces <i>INCREASE</i> Study of Tyvaso® Meets Primary and All Secondary Endpoints (Feb. 24, 2020) (UTC LIQ00063612)
Excerpt of Charles H. Hennekens & Julie E. Buring, <i>Epidemiology in Medicine</i> (Sherry L Mayrent ed., 1987)
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Kallmes DF et al., <i>A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures</i> , 361 N. Eng. J. Med. 569 (2009)
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<p> <a href="#">Supplementary Material 1 for Steven D. Nathan et al., <i>Inhaled Treprostinil in Pulmonary Hypertension Associated With COPD: PERFECT Study Results</i>, 63 Eur. Respiratory J. (2024)</a> </p>
<p> <a href="#">Supplementary Material 2 for Steven D. Nathan et al., <i>Inhaled Treprostinil in Pulmonary Hypertension Associated With COPD: PERFECT Study Results</i>, 63 Eur. Respiratory J. (2024)</a> </p>

# EXHIBIT 2



**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

UNITED THERAPEUTICS  
CORPORATION,

Plaintiff

V.

LIQUIDIA TECHNOLOGIES, INC.,

Defendant.

C.A. No. 1:23-cv-00975-RGA

**REPLY EXPERT REPORT OF RONALD A. THISTED, PH.D.  
REGARDING INFRINGEMENT OF U.S. PATENT NO. 11,826,327**

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### **TABLE OF ABBREVIATIONS**

<b>Patent Documents</b>	
'327 patent	U.S. Patent No. 11,826,327 (UTC PH-ILD_005310)
<b>Expert Reports/Declarations</b>	
Channick Op. Rept.	2024-12-20 Expert Report of Dr. Richard Channick
Channick Reb. Rpt.	2025-01-23 Rebuttal Expert Report of Dr. Richard Channick
Nathan PI Decl.	2024-02-26 D.I. 28 Declaration of Steven D. Nathan, M.D.
Nathan Op. Rpt.	2024-12-20 Expert Report of Steven D. Nathan, M.D.
Thisted Reb. Rpt.	2025-01-23 Rebuttal Report of Ronald A. Thisted, Ph.D.
<b>Litigation Materials</b>	
Deng Dep. Tr.	2024-11-12 Chunqin Deng Deposition Transcript
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<b>Literature</b>	
Faria-Urbina 2018	UTC PH-ILD_009936
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Roscigno 2021	UTC PH-ILD_010665
Thabane 2013	UTC PH-ILD_227534
<b>Other</b>	
2009 Tyvaso Label	UTC PH-ILD_010692
2022 Tyvaso DPI Label	UTC PH-ILD_010709
2022 Tyvaso Label	UTC PH-ILD_005268
Amended Proposed Label	LIQ PH-ILD_00091129
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ASCENT at Clinical Trials	UTC PH-ILD_000395
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Yutrepia Label	LIQ_PH-ILD_00126017
Yutrepia Marketing Diagram	LIQ_PH-ILD_00147156
Yutrepia Marketing Handout	LIQ_PH-ILD_00147141
Yutrepia PH-ILD sNDA	LIQ_PH-ILD_00091023
Yutrepia Presentation	LIQ_PH-ILD_00147196

## I. INTRODUCTION

1. My name is Ronald A. Thisted, Ph.D. I previously submitted the January 23, 2025 Rebuttal Report of Ronald A. Thisted, Ph.D. (“Rebuttal Report” or “Thisted Reb. Rpt.”) in the above-captioned litigation. That document is herein incorporated by reference in its entirety.<sup>1</sup>

2. As I explained in my Rebuttal Report, UTC has asserted that Defendant Liquidia Technologies, Inc. (“Liquidia”) infringes several claims of U.S. Patent No. 11,826,327 (“the ’327 patent”).<sup>2</sup> I understand that UTC has asserted infringement of claims 1-11 and 14-19 of the ’327 patent (“Asserted Claims”) based on Liquidia’s submission of an application to the U.S. Food and Drug Administration (FDA) to commercially manufacture, use, market, and/or sell Yutrepia in the United States “for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability”<sup>3</sup> (“PH-ILD”). I further understand that UTC has asserted infringement based on Liquidia’s conduct in conducting a clinical trial known as “An Open-Label Prospective Multicenter Study to Evaluate Safety and Tolerability of Dry Powder Inhaled Treprostinil in Pulmonary Hypertension” (“ASCENT”).

3. I have reviewed the Opening Expert Report of Steven D. Nathan, M.D. Regarding Infringement of U.S. Patent No. 11,826,327, dated December 20, 2024 (“Dr. Nathan’s Opening Report” or “Nathan Opening Rpt.”). I have also reviewed the Rebuttal Expert Report of Dr. Richard Channick in Response to the Initial Expert Report of Dr. Steven Nathan, dated January 23, 2025 (“Dr. Channick’s Rebuttal Report” or “Channick Rep. Rpt.”). In Dr. Channick’s Rebuttal Report, he explained that, in his opinion, Liquidia has not and will not induce or directly infringe,

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<sup>1</sup> For clarity, I refer to my Rebuttal Report along with this Reply Report as “my Reports,” collectively.

<sup>2</sup> Thisted Reb. Rpt. ¶ 1.

<sup>3</sup> Yutrepia Label at 126021, for clarity I may interchangeably refer to “Yutrepia’s tentatively approved label” or o “Yutrepia’s proposed label” or “the tentatively approved Yutrepia Label” or “the proposed Yutrepia label” or just as the “Yutrepia Label.”

and that neither healthcare providers nor patients will directly infringe, any of the Asserted Claims.<sup>4</sup> I have been asked by UTC to provide my expert opinion in reply to Dr. Channick's Rebuttal Report regarding whether Liquidia's Yutrepia product infringes and, if approved by FDA for commercial manufacture, use, marketing, and/or sale in the United States, will infringe the Asserted Claims of the '327 patent. As explained in greater detail below, I disagree with the opinions expressed in Dr. Channick's Rebuttal Report and I believe that each Asserted Claim has been infringed, is currently infringed, and will be infringed by Liquidia, healthcare providers, and/or patients.

4. I understand that I may be expected to testify on these opinions, as set forth in this Reply Report, and in any Supplemental Expert Reports that I may prepare for this case in the future. I also understand that I may be expected to testify with respect to arguments raised by Liquidia in its Opening or Rebuttal Reports or matters addressed by any expert testifying on behalf of Liquidia, for example in response to this Reply Report.

5. I reserve the right to supplement or modify the opinions expressed in this Reply Report, as well as the basis for my opinions, depending on the nature and content of the proofs presented by Liquidia and any other information subsequently provided by Liquidia, Liquidia's expert(s), and/or discovered by UTC. I further reserve the right to use animations, demonstratives (including, for example, a graphical representation of information otherwise disclosed in my Reports), enlargements of actual exhibits, and other information in order to illustrate my opinions.

**A. Qualifications, Prior Testimony, and Compensation**

6. My qualifications, a list of cases in which I provided expert testimony at trial or by deposition, and my compensation are set forth in or attached to my Rebuttal Report.<sup>5</sup> This

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<sup>4</sup> Channick Reb. Rpt. § V (¶¶ 46-165).

<sup>5</sup> Thisted Reb. Rpt. ¶¶ 6-20, Ex. B.

information has not changed since I submitted my Rebuttal Report and are incorporated by reference here.

7. In addition to my qualifications detailed in my Rebuttal Report, I add that my experience consulting with the pharmaceutical and medical device industries since the late 1970s has included interacting with FDA biostatisticians and medical reviewing officers to ensure that FDA's regulatory requirements could be met, participating in pre-NDA and pre-Phase III meetings with FDA as part of the drug sponsor's team, and participating in conference calls with FDA Divisional leadership in responding to non-approvable letters.<sup>6</sup> I have also conducted analyses of bioavailability and bioequivalence studies submitted for regulatory approval in the United States (Food and Drug Administration), Europe (European Medicines Agency), and Australia (Therapeutic Goods Agency).

**B. Materials Considered and Bases for My Opinions**

8. In conducting my analysis and reaching the conclusions described in this report, I have considered the materials cited in this report, my Rebuttal Report and the materials cited therein, which are listed in **Exhibit C** of my Rebuttal Report, as well as Dr. Nathan's Opening Report, Dr. Channick's Rebuttal Report, and the materials cited in those reports. A complete list of all documents and materials that I have considered in preparing this report are attached here as **Exhibit D**. In addition, I have further relied on my knowledge, education and training and my many years of experience in the fields of biostatistics and epidemiology, as reflected in my qualifications and credentials set forth in my Rebuttal Report and in my *curriculum vitae*.

9. I intend the full page range of all documents and materials cited in this report to be part of this report. To the extent I cite to only certain portions of a reference, I reserve the right to

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<sup>6</sup> Thisted Reb. Rpt. ¶¶ 6-19.

rely on the entirety of that reference. Where I cite a particular figure or chart, the citation should be understood to encompass any text referring or relating to that figure or chart, in addition to the figure or chart itself. Similarly, where a cited portion of text refers to a figure or chart, the citation should be understood to include the figure or chart as well. I also rely on my knowledge to provide context, and to aid in understanding and interpreting the portions of the evidence that are cited.

**C. Assignment and Summary of My Opinions**

10. UTC has asked me to analyze and respond to the opinions offered in Dr. Channick's Rebuttal Report regarding infringement of the '327 patent. As explained in greater detail below and throughout this report, I disagree with Dr. Channick's opinions and analysis. In summary, it is my opinion that:

11. Dr. Channick is wrong that healthcare providers and patients will not directly infringe of each of the Asserted Claims of the '327 patent by administering Yutrepia to PH-ILD patients according to the Yutrepia label.

12. Dr. Channick is wrong that Liquidia will not induce infringement of each of the Asserted Claims of the '327 patent by instructing or otherwise encouraging healthcare providers and patients to administer Yutrepia to PH-ILD patients according to the Yutrepia label.

13. Dr. Channick is wrong that healthcare providers and patients involved in the ASCENT trial have not infringed and will not continue to infringe each of the Asserted Claims of the '327 patent by administering Yutrepia to PH-ILD patients according to the ASCENT Protocols.

14. Dr. Channick is wrong that Liquidia has not induced and will not continue to induce infringement of each of the Asserted Claims of the '327 patent by instructing or otherwise encouraging healthcare providers and patients to administer Yutrepia according to the ASCENT Protocols.

15. Dr. Channick continues to mischaracterize what was in the public domain and ignores that INCREASE was the first randomized, well-controlled clinical trial showing a definitive treatment effect in PH-ILD patients administered inhaled treprostinil.

16. Dr. Channick's opinion that the findings of the INCREASE study do not apply to PH-ILD patients administered Yutrepia ignores the Yutrepia label itself, contradicts Liquidia's representations to the FDA, devalues the comparative pharmacokinetic study between Tyvaso and Yutrepia, and misunderstands the statistical impact of the INCREASE study results.

17. Dr. Channick's opinion that in order to infringe each of the Asserted Claims of the '327 patent, a physician would need to measure and assess statistical and clinical outcomes is not consistent with the plain language of the Asserted Claims, which are satisfied by the administration of Yutrepia to PH-ILD patients in view of the INCREASE trial results that Yutrepia's approval for its PH-ILD indication relies upon.

## **II. LEGAL PRINCIPLES**

18. As mentioned in my Rebuttal Report, I am not a lawyer nor an expert in patent law.<sup>7</sup> Therefore, I offer no legal opinion in this report. Counsel have advised me as to various legal standards applicable to the issues I address in this report, and I have applied those standards in conducting my analysis and in reaching my conclusions.

### **A. Person of Ordinary Skill in the Art and Claim Construction**

19. Counsel have advised me that patent infringement is evaluated from the perspective of a hypothetical person of ordinary skill in the art ("POSA"). In conducting my analysis and reaching my conclusions herein, I have applied the definition of a POSA that I have set forth in

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<sup>7</sup> Thisted Reb. Rpt. ¶ 25.

my Rebuttal Report.<sup>8</sup> I incorporate my discussion of the POSA from my Rebuttal Report as if fully set forth here.

20. Counsel have also explained that patent infringement is assessed under a two-step inquiry. The first step is to construe the language of the claims to establish their scope and meaning. I provided a discussion of the claim construction from this case in my Rebuttal Report and thus incorporate that discussion by reference here.<sup>9</sup> Then, each construed claim asserted by the patentee is compared to the product or method accused of patent infringement to determine whether it practices (and thus infringes) the claim.

## **B. Patent Infringement**

21. I understand from counsel that patent infringement is assessed at the time when the alleged infringement occurs. I understand that this is a different frame of reference from patent validity, which as discussed in my Rebuttal Report, is evaluated as of the filing date of the patent.<sup>10</sup>

22. I am informed by counsel that UTC must prove infringement by a preponderance of the evidence. I understand that the preponderance of the evidence standard means that UTC must show that it is more likely than not that Liquidia has infringed the '327 patent. Counsel has also explained that my opinions regarding infringement should be based on the proposed drug product for which Liquidia has sought FDA approval to commercially market and sell in the United States, i.e., Yutrepia™. In evaluating Liquidia's proposed Yutrepia™ product for infringement, I understand that I should conduct my analysis on a claim-by-claim basis and primarily consider the new drug application submitted by Liquidia for review by FDA, including the proposed prescribing information (i.e., label), along with any other proposed or actual marketing information.

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<sup>8</sup> Thisted Reb. Rpt. ¶¶ 29-33.

<sup>9</sup> Thisted Reb. Rpt. ¶¶ 32, 268.

<sup>10</sup> Thisted Reb. Rpt. § VI.A.

23. I also understand that patent claims may be infringed “directly” or “indirectly.” I will address each in turn. First, to prove “direct infringement” of a patented method, UTC must show that Liquidia practices (or will practice) each step of the patent claim in the United States. However, counsel has explained that a patentee may successfully demonstrate direct infringement of a method claim even if the method accused of infringement does not practice each step of the claimed method all the time. Instead, I understand that I may find infringement if the method accused of infringement practices the steps of the claimed method only some of the time.

24. For example, I am informed that I may find that a healthcare provider is liable for direct infringement if he or she prescribed a medication to a patient based on the drug’s approved prescribing information, and then that patient self-administered the medication in a manner that practices the steps of a claimed method of treatment. I understand that this means, in other words, that where a physician directs the manner and timing in which a patient administers a medication, any direct infringement of the patient can be attributed to the healthcare provider.

25. Second, counsel has explained that a party “indirectly infringes” a patented method when it acts in a particular manner that encourages a third party to infringe. I am told that there are several types of indirect infringement, one of which is known as “induced infringement.” In the context of induced infringement, I understand that a party is liable when it “induces” (or will “induce”) a third party to directly infringe (i.e., perform) the steps of the patented method. For example, I am told that a pharmaceutical company may be liable for induced infringement for manufacturing or marketing a drug that directly infringes a claimed method of treatment when a physician instructs a patient to administer the drug or when a patient administers the drug to themselves. I am also informed that I may find induced infringement even if the accused infringer held a subjective belief that the asserted patent claim is invalid. In other words, a patent claim may

be infringed regardless of whether the same claim is later proven to be invalid in a court of law. I understand this to be the case because, as counsel has explained, patent infringement and patent invalidity require separate analyses and demand different levels of proof.

26. To find induced infringement, I must find that each of the following requirements are satisfied: (1) a third party committed an act of direct infringement; (2) Liquidia, at some point after the '327 patent issued, acted with the intent to cause, and in a manner that led to, the third party's act of direct infringement; and (3) Liquidia took such action despite its awareness of the '327 patent and notwithstanding its knowledge that the third party's actions, if carried out, would directly infringe the methods claimed by the '327 patent.

27. However, I am informed that I may find induced infringement even if there is no direct evidence of Liquidia's intent to induce the direct infringement of another. In other words, I am told that I may form my opinions based on circumstantial evidence of intent to induce infringement such as proposed prescribing information that encourages, recommends, or promotes the infringement of another. I am also told that I may consider marketing materials and press releases when analyzing whether there is circumstantial evidence of intent to induce infringement. For example, I understand these requirements to mean that a pharmaceutical company could be liable for induced infringement if it encourages, recommends, or promotes physicians or patients to administer a drug product in a way that infringes a claimed invention.

**C. The § 271(e)(1) Safe Harbor**

28. Notwithstanding the legal framework for patent infringement that has been explained to me and that which I have summarized above, I have also been informed that some activities related to pharmaceutical development that would otherwise count as infringement (e.g., because they involve the commercial manufacture, use, or sale of a product or method claimed in a patent), are protected by a "safe harbor" law. Counsel has explained that the definition of "safe

harbor” is defined in Title 35, section 271(e)(1) of the United States Code, which I have reproduced below:

It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

29. Counsel has also explained that the safe harbor described in the paragraph above protects conduct that would otherwise count as patent infringement if the conduct was, for example, undertaken solely for uses that are reasonably related to submitting information to FDA for obtaining regulatory approval of a drug product (such as in a new drug application or abbreviated new drug application). I also understand from counsel that the safe harbor would not protect infringing conduct that is not reasonably related to obtaining regulatory approval of a drug product, but merely related to the routine collection and reporting of information to FDA. For example, I have learned from counsel that collecting and reporting information related to a drug product’s safety, without more, would not satisfy the safe harbor’s requirements. Ultimately, as counsel has explained, the application of the safe harbor depends on the extent to which the conduct is reasonably related to obtaining regulatory approval of a drug product.

### **III. SCIENTIFIC AND TECHNICAL BACKGROUND**

30. If asked to testify, I may provide a tutorial on the background facts and scientific opinions that support my opinions. I reserve the right to provide additional background information or detail as appropriate.

**A. Pulmonary Hypertension**

31. I reviewed a public, redacted version of a declaration of Dr. Nathan to learn about pulmonary hypertension, varieties thereof, and treatment options.<sup>11</sup>

**B. Principles of Study Design and Statistics**

32. I discussed principles of study design and statistics in my Rebuttal Report, which I incorporate herein by reference.<sup>12</sup>

33. Dr. Nathan discusses the interpretation of the terms “statistical significance” and “p-value” in his opening report, opining:

Statistical significance helps determine whether an observed effect or pattern in data is likely caused by the intervention rather than random chance. This is often assessed using a p-value, which measures the probability of seeing the observed results if there were no real effect. A p-value less than 0.05 is generally understood to be statistically significant, meaning the effect is unlikely to be due to chance. A p-value greater than 0.05 means there is not enough evidence to confidently say the result is significant—it could be due to random variation.<sup>13</sup>

Dr. Nathan’s interpretation is discussed in the context of results from the INCREASE study—a multicenter, randomized (1:1 inhaled treprostinil:placebo), double-blinded, placebo-controlled clinical trial—that enrolled PH-ILD patients and compared the effects of treatment with inhaled treprostinil to the effects of treatment with a placebo, which I discussed in my Rebuttal Report and in further detail below.<sup>14</sup> In this context (and in all of Dr. Nathan’s subsequent discussions of statistical significance and p-values), Dr. Nathan’s interpretation of determining whether an observed pattern or effect is likely caused by the intervention as opposed to random chance is

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<sup>11</sup> Nathan PI Decl.

<sup>12</sup> Thisted Reb. Rpt. § VII.

<sup>13</sup> Nathan Op. Rpt. ¶ 68.

<sup>14</sup> *Infra* § III.D.2; Thisted Reb. Rpt. §§ X.A, XI.A; e.g., INCREASE publication (UTC\_PH-ILD\_010790) at -790.

appropriate and correct.<sup>15</sup> Moreover, Dr. Nathan’s interpretation is consistent with the discussion of statistical significance in my Rebuttal Report.<sup>16</sup>

34. Dr. Channick’s Rebuttal Report also offers interpretations of “statistical significance” and “p-value.” Dr. Channick states:

As Dr. Nathan acknowledges, a statistically significant result is one that is unlikely to have occurred by chance alone. To determine if the result of a particular intervention is statistically significant, a person must select a parameter to measure, apply the intervention to a sufficiently large group to detect a meaningful difference, measure the selected parameter in each group member, aggregate the collected data, and perform statistical analysis on the data. I understand that the Court agrees that finding “statistical significance requires data from multiple patients.” Part of conducting a statistical significance analysis includes calculating a p-value, which indicates the probability of obtaining the observed results by chance. A low p-value, generally one less than 0.05, suggests that the results are unlikely to have happened by random chance and are more likely due to the intervention taken. In general, statistical significance indicates that the result is reliable, reproducible, and attributable to the intervention’s effects. [footnotes omitted]<sup>17</sup>

Dr. Channick’s interpretations of p-values and statistical significance cannot be applied—and are incorrect—in the context of nonrandomized or noncomparative clinical studies, which appears to be what Dr. Channick’s Rebuttal Report does, and thus Dr. Channick’s statements also appear to mischaracterize Dr. Nathan’s statements.<sup>18</sup> As I explained in my Rebuttal Report, p-values generated when analyzing nonrandomized or noncomparative clinical studies are merely descriptive measures that have no necessary relationship to the role of chance as a possible

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<sup>15</sup> See Thisted Reb. Rpt. § VII.

<sup>16</sup> See Thisted Reb. Rpt. § VII.

<sup>17</sup> Channick Reb. Rpt. ¶ 60.

<sup>18</sup> Channick Reb. Rpt. § V.B.1; see Thisted Reb. Rpt. § VII. To obtain a p-value in a randomized clinical trial, one must apply *both the intervention of interest and a suitable control intervention* to a sufficiently large group. In the context of a randomized clinical trial, the p-value indicates the probability of obtaining a result *at least as large* as those observed purely by random chance.

explanation of observed effects.<sup>19</sup> That is because the design of those studies does not explicitly include any chance mechanism that *could* account for observed study effects.<sup>20</sup> Consequently, any statements of statistical significance of effects observed in such studies are merely statements that the p-value, when computed, fell below the customary threshold of 0.05.<sup>21</sup>

35. As discussed in detail below, in the context of nonrandomized noncomparative studies, Dr. Channick’s opinion that “statistical significance indicates that the result is reliable, reproducible, *and attributable to the intervention’s effects*,”<sup>22</sup> is simply not true.<sup>23</sup>

### **C. Drug Approval**

36. To receive approval from the U.S. Food and Drug Administration (“FDA”) to commercially market a drug product in the United States, a sponsor must demonstrate substantial evidence that the drug is safe and effective for its intended use. Further, to establish substantial evidence of safety and effectiveness, the sponsor may rely on one of several drug approval pathways. The sponsor may submit a new drug application (“NDA”), known as a “stand-alone NDA” under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (“FDCA”), an abbreviated NDA (“ANDA”) under section 505(j) of the FDCA, or a hybrid version that borrows aspects from both the 505(b)(1) and 505(j) approval pathways, known as the section 505(b)(2) NDA.<sup>24</sup>

37. Drug sponsors seeking approval to market a new, never previously approved drug product typically submit a full “stand-alone NDA” under the section 505(b)(1) approval pathway.

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<sup>19</sup> Thisted Reb. Rpt. §§ VII, IX.B-E, XI, XV.

<sup>20</sup> *Id.*

<sup>21</sup> *Id.*

<sup>22</sup> Channick Reb. Rpt. ¶ 60 (emphasis added).

<sup>23</sup> Thisted Reb. Rpt. §§ VII, IX.B-E, XI, XV.

<sup>24</sup> U.S. Food & Drug Admin., Determining Whether to Submit an ANDA or a 505(b)(2) Application: Guidance for Industry (2019) (UTC\_PH-ILD\_227401) at -404, -405.

To successfully file a 505(b)(1) NDA, the sponsor must include full reports of investigations conducted or licensed by the sponsor to establish the substantial evidence of safety and effectiveness requirement. Such reports of investigations typically include nonclinical toxicology and carcinogenicity data, clinical pharmacology data, clinical safety and effectiveness data, and reports relating to chemistry, manufacturing, and controls. In addition, among other things, the 505(b)(1) drug sponsor must submit a proposed version of the prescribing information (i.e., “label” or “package insert” or “PI”) for review and approval by FDA.

38. In contrast to the section 505(b)(1) approval pathway, drug applicants seeking approval to market a drug product that has been previously approved in the United States (i.e., a generic drug product) typically file an ANDA under the section 505(j) of the FDCA. An ANDA applicant is permitted to rely entirely on reports of investigations submitted by another drug sponsor for the approval of another drug product (i.e., “reference listed drug”) that is bioequivalent and therapeutically equivalent to the proposed generic drug product. This means that the generic drug applicant essentially relies on FDA’s prior determination that the reference listed drug is safe and effective for its approved use. Among other things, the generic drug applicant must also demonstrate that the proposed label is the same as the label that was previously approved for the reference listed drug.

39. As mentioned above, the section 505(b)(2) approval pathway is “hybrid” in that it does not require full reports of investigations like the 505(b)(1) approval pathway, but, unlike the 505(j) approval pathway, requires some reports of investigations beyond a showing of bioequivalence. An applicant would consider submitting a 505(b)(2) application if it does not wish to conduct sufficient investigations to satisfy the requirements of the 505(b)(1) approval pathway but seeks to introduce a drug product that has intentional differences from a reference listed drug

such that the applicant would be ineligible to submit an ANDA.<sup>25</sup> For example, an applicant seeking to rely on prior reports of investigations to seek approval of a proposed drug product with a different formulation than the reference listed drug would be ineligible for the 505(j) pathway and thus would likely seek approval by way of a section 505(b)(2) application.<sup>26</sup>

40. A sponsor seeking approval via the 505(b)(2) pathway for a drug product that shares certain features with a previously FDA-approved drug must still demonstrate that the proposed drug product is safe and effective for its intended use and provide a proposed version of the drug label for review by FDA. However, unlike the 505(b)(1) NDA, at least some of the reports of investigations are studies that were conducted and submitted for a different, previously FDA-approved drug product (known as the “reference listed drug” or “RLD”).<sup>27</sup> In other words, 505(b)(2) applicants may rely on FDA’s prior finding(s) of safety and/or effectiveness for one (or more) listed drug(s), if doing so is scientifically appropriate.<sup>28</sup> Sponsors of 505(b)(2) drug products may “reference” (in other words, rely on) studies concerning, for example, clinical pharmacology, clinical safety, and/or clinical efficacy.<sup>29</sup>

41. To support the scientific appropriateness of relying on FDA’s prior finding(s) of safety and/or efficacy for a listed drug, 505(b)(2) applicants must demonstrate, to FDA’s satisfaction, an adequate “bridge” between the proposed drug product and the previously approved drug.<sup>30</sup> Further, the “bridge” may be established through a finding that the proposed and previously

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<sup>25</sup> See U.S. Food & Drug Admin., Determining Whether to Submit an ANDA or a 505(b)(2) Application: Guidance for Industry (2019) (UTC\_PH-ILD\_227401) at -413.

<sup>26</sup> See *id.*

<sup>27</sup> FDA Response (LIQ\_PH-ILD\_00120424) at -430.

<sup>28</sup> FDA Response (LIQ\_PH-ILD\_00120424) at -429.

<sup>29</sup> Beth Goldstein, Sci. Pol’y Analyst, U.S. Food & Drug Admin., Overview of the 505(b)(2) Regulatory Pathway for New Drug Applications (UTC\_PH-ILD\_227379) at -385, -386.

<sup>30</sup> FDA Response (LIQ\_PH-ILD\_00120424) at -429, -430.

approved drug products share similar bioavailability (i.e., through a comparative bioavailability study).<sup>31</sup> I am also aware that a sponsor seeking approval via the 505(b)(2) pathway must also include—in addition to establishing the bridge—sufficient data to support any modifications to the listed drug (i.e., differences between the proposed drug product and the reference listed drug such as changes in dosage form).<sup>32</sup>

42. Demonstrating biocomparability or bioequivalence entails comparing the two drug products' respective bioavailability—the amount of a drug product's active ingredient that gets absorbed into the blood stream and the timing of absorption when administered. Bioavailability is ordinarily assessed using healthy subjects and is ordinarily evaluated by measuring certain pharmacokinetic parameters, specifically  $C_{\max}$  (the maximum concentration in the blood achieved after a single administration) and  $AUC_{\infty}$  (roughly, the total amount of drug in the blood stream over time). According to FDA, bioequivalence can be established for ANDAs when the bioavailability of a generic drug is demonstrated not to fall below 80% nor exceed 125% the bioavailability of the RLD. The same principle applies to products FDA approves by the 505(b)(2) mechanism, in which the applicant seeking approval of a new proposed product is permitted to rely on some data (such as clinical outcomes) demonstrated by a reference listed drug, but only if the applicant first demonstrates a sufficient “bridge” between its new product and the RLD, e.g., with a biocomparability study.

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<sup>31</sup> Beth Goldstein, Sci. Pol'y Analyst, U.S. Food & Drug Admin., Overview of the 505(b)(2) Regulatory Pathway for New Drug Applications (UTC\_PH-ILD\_227379) at -384; FDA Response (LIQ\_PH-ILD\_00120424) at -429.

<sup>32</sup> U.S. Food & Drug Admin., Determining Whether to Submit an ANDA or a 505(b)(2) Application: Guidance for Industry (2019) (UTC\_PH-ILD\_227401) at -407, -408; FDA Response (LIQ\_PH-ILD\_00120424) at -429.

43. As mentioned above, 505(j) and 505(b)(2) applicants must submit to FDA and obtain approval with respect to the label for its proposed drug product. The product label which is approved for a drug product provides the information that clinicians need to know in order to prescribe the product, and that patients need to know to use the product. In other words, the purpose of the labelling requirement as it relates to FDA approval of drug products is to facilitate the prescribing decisions of physicians or other healthcare providers.<sup>33</sup> The “principal objective of labeling is to provide the information that is most useful to prescribers in treating their patients.”<sup>34</sup> An approved drug label typically includes information such as, for example, the drug’s indication of use, dosage and administration, dosage forms and strengths, contraindications, warnings and precautions, and adverse reactions.<sup>35</sup> In addition, the drug label must discuss the clinical investigations that were conducted to establish the drug’s efficacy for its approved indication.<sup>36</sup> “This is usually accomplished by providing concise, accurate summaries of information from studies concerning [the] drug’s effectiveness (and sometimes safety) that practitioners [would] consider important to clinical decision making.”<sup>37</sup>

44. The indications listed in a drug product’s label are the only indications for which the sponsor is legally permitted to market the drug product. In the case of an applicant seeking

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<sup>33</sup> U.S. Food & Drug Admin., Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (2013) (UTC\_PH-ILD\_227418) at -423.

<sup>34</sup> U.S. Food & Drug Admin., Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (2006) (UTC\_PH-ILD\_227354) at -357.

<sup>35</sup> U.S. Food & Drug Admin., Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (2013) (UTC\_PH-ILD\_227418) at -448.

<sup>36</sup> U.S. Food & Drug Admin., Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (2006) (UTC\_PH-ILD\_227354) at -358.

<sup>37</sup> *Id.*

approval for a drug product through the 505(j) or 505(b)(2) approval pathway, the proposed product's label may recite the RLD's indications for which the applicant is fully or partially relying on FDA's finding that the RLD is safe and effective, i.e., the applicant may rely fully or in part on the clinical data that were generated for (and submitted to FDA with respect to) the RLD. When an applicant seeks approval for a drug product by relying on the RLD's clinical efficacy or safety data, that applicant is acknowledging that its product will also provide the same clinical efficacy and safety when administered according to the label, i.e., the applicant attaches the RLD's results to its proposed product to the extent the applicant relies on the RLD's clinical data for approval.<sup>38</sup> This reliance is also reflected in the proposed drug product's label, e.g., the language of the listed indications, the dosage and administration information, the clinical trials summarized, and so on. In particular, this reliance indicates that—were clinical trials conducted with the proposed new drug product that were similar in design and conduct to those reported by the RLD sponsor—these hypothetical clinical trials would be expected to produce results identical to (or nearly identical to) those generated from the relied upon RLD studies, including the statistically significant treatment effects that the RLD studies identify as well as the magnitude of those effects. It is for this reason that FDA does not require a new product's applicant to reproduce the already approved RLD's

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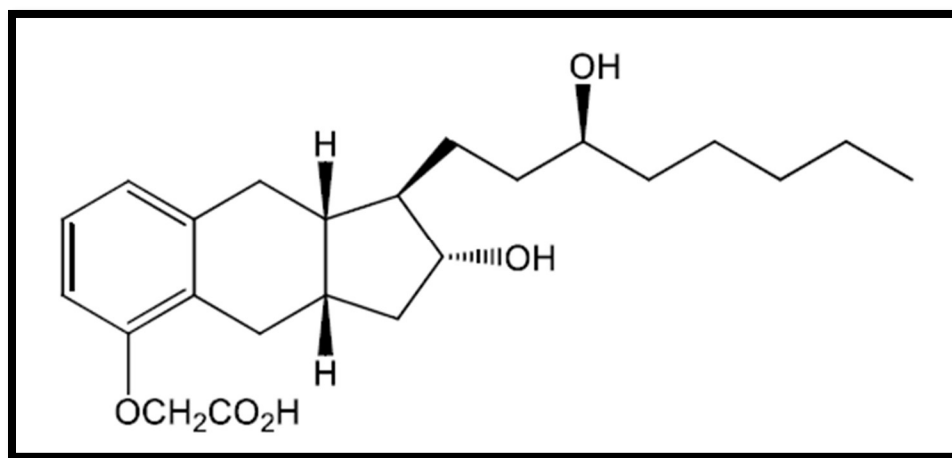
<sup>38</sup> See U.S. Food & Drug Admin., Guidance for Industry: Applications Covered by Section 505(b)(2): Draft Guidance (1999) (UTC\_PH-ILD\_227310) at -314, -315 (“[R]el[ying] on the Agency’s previous finding of safety and/or effectiveness for a drug ... essentially makes the Agency’s conclusions that would support the approval of a 505(j) application available to an applicant who develops a modification of a drug. Section 314.54 permits a 505(b)(2) applicant to rely on the Agency’s finding of safety and effectiveness for an approved drug to the extent such reliance would be permitted under the generic drug approval provisions at section 505(j). This approach is intended to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug while protecting the patent and exclusivity rights for the approved drug.”); see also 21 C.F.R. § 314.54(a)(1)(iii)(A) (“The listed drug(s) identified as relied upon must include a drug product approved in an NDA that[] [i]s pharmaceutically equivalent to the drug product for which the original 505(b)(2) application is submitted[.]”).

clinical data—assuming that bioequivalence is demonstrated in the case of the 505(j) pathway or appropriate bridges including comparable bioavailability are established in the case of the 505(b)(2) pathway—it would be a redundant and unnecessary exercise.

**D. United Therapeutics’ Tyvaso products indicated for PH-ILD to improve exercise ability**

**1. United Therapeutics’ Tyvaso products**

45. United Therapeutics currently offers two inhaled treprostinil products—Tyvaso and Tyvaso DPI. Tyvaso is formulated as a liquid solution and is delivered to patients with an ultrasonic, pulsed-delivery nebulizer. Tyvaso DPI is formulated as a dry powder and is delivered to patients with a dry powder inhaler. Scientific studies submitted to the FDA have shown that Tyvaso and Tyvaso DPI have comparable pharmacokinetic profiles. Treprostinil is a prostacyclin mimetic with the following chemical structure:



46. Tyvaso was approved in July 2009 for the treatment of PAH following the TRIUMPH study. The PH-ILD indication was added to the Tyvaso label in 2021 following the INCREASE study, which is discussed in further detail below.<sup>39</sup>

<sup>39</sup> *Infra* § III.D.2.

47. Tyvaso DPI was approved in both the PAH and PH-ILD indications following the BREEZE study. The Breeze study evaluated the safety and tolerability of Tyvaso DPI during a 3-week treatment phase in patients previously treated with Tyvaso.<sup>40</sup> The study (including the long-term extension phase) concluded that the safety profile of Tyvaso DPI “was consistent with the expected known safety profile of Tyvaso.”<sup>41</sup>

## **2. The INCREASE Study**

48. I incorporate by reference my description of the INCREASE study and related opinions from my Rebuttal Report submitted in this matter dated January 23, 2025.<sup>42</sup>

49. The INCREASE study, sponsored by United Therapeutics and assigned ClinicalTrials.gov. number NCT02630316, was conducted with the objective of “evaluat[ing] the safety and efficacy of inhaled treprostinil in patients with pulmonary hypertension due to interstitial lung disease.”<sup>43</sup> The study was initiated on February 3, 2017, completed on December 26, 2019, and the results were published in the New England Journal of Medicine on January 13, 2021.<sup>44</sup> It was the first randomized controlled clinical trial to evaluate the use of inhaled treprostinil in PH-ILD patients.

50. The study randomly assigned patients to treatment with Tyvaso or placebo and followed them through the 16-week treatment period.<sup>45</sup> A number of parameters were measured on a fixed schedule throughout the duration of the study. These parameters included 6MWD,

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<sup>40</sup> 2022 Tyvaso DPI Label (UTC\_PH-ILD\_010709) at -712.

<sup>41</sup> *Id.*

<sup>42</sup> Thisted Reb. Rpt. § X, XI.

<sup>43</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -791.

<sup>44</sup> INCREASE CSR (UTC\_PH-ILD\_055371) at -371; INCREASE publication (UTC\_PH-ILD\_010790) at -790.

<sup>45</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -792.

plasma concentration of NT-proBNP, FVC, occurrence of clinical worsening events due to interstitial lung disease, and occurrence of exacerbations due to interstitial lung disease.

**a. Study design**

51. The trial population of the INCREASE study consisted of patients diagnosed with pulmonary hypertension associated with interstitial lung disease.<sup>46</sup> Interstitial lung disease was determined based on evidence of diffuse parenchymal lung disease on computed tomography of the chest performed within 6 months before randomization.<sup>47</sup> The hemodynamic inclusion criteria were as follows: PVR > 3 Wood units, wedge pressure  $\leq$  15 mm Hg, and mPAP  $\geq$  25 mm Hg as measured by right heart catheterization within one year of randomization.<sup>48</sup> Patients with a 6MWD less 100m were excluded, and patients with connective tissue disease were excluded unless they had a percent predicted forced vital capacity less than 70%.<sup>49</sup>

52. Any patients receiving an approved therapy for pulmonary arterial hypertension within 60 days before randomization were excluded.<sup>50</sup> Also, any patients who were taking drug treatments for their underlying lung disease were excluded if they were not receiving a stable dose for at least 30 days before randomization.<sup>51</sup>

53. Subject disposition is summarized as follows:

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<sup>46</sup> *Id.* at -791.

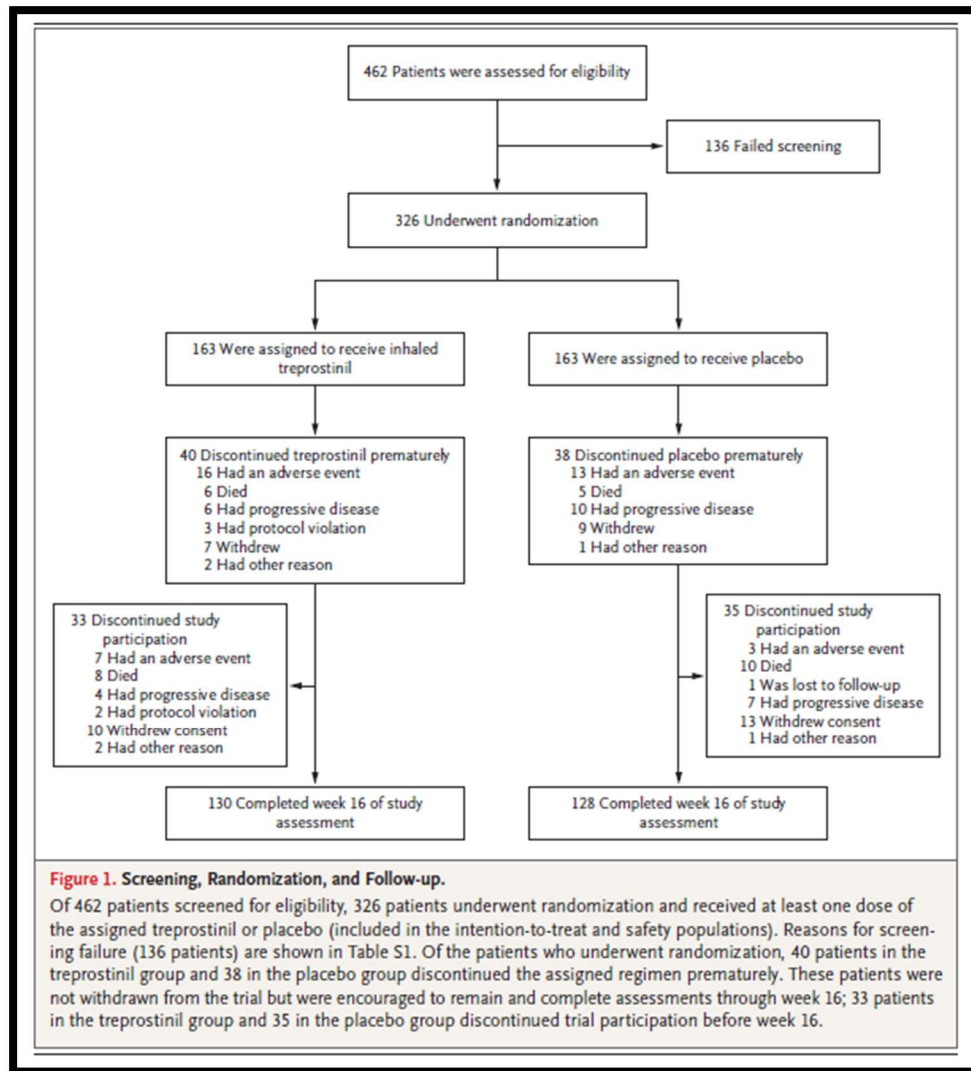
<sup>47</sup> *Id.*

<sup>48</sup> *Id.*

<sup>49</sup> *Id.*

<sup>50</sup> *Id.* at -791-792.

<sup>51</sup> *Id.* at -791.



54. Following randomization, patients in the treatment arm were administered inhaled treprostinil at a concentration of 0.6 mg/mL corresponding to 6 µg per breath.<sup>52</sup> These subjects were dosed as follows:<sup>53</sup>

<sup>52</sup> *Id.* at -792.

<sup>53</sup> INCREASE Protocol (UTC\_PH-ILD\_145360) at -470-471.

Once informed consent has been signed, all entry criteria have been met, and the randomized treatment assignment confirmed, the first dose of study drug (3 breaths; 18 mcg) will be inhaled in the clinic, followed by at least a 1 hour observation period (defined as Day 1). Study drug doses should be maximized throughout the study, dose escalations (additional 1 breath 4 times daily) can occur up to every 3 days with a target dosing regimen of 9 breaths (54 mcg) 4 times daily and a maximum dose of 12 breaths (72 mcg) 4 times daily within 4 weeks of beginning the treatment, as clinically tolerated. Table 6-1 provides a guideline for the recommended dose escalations.

**Table 6-1 Recommended Inhaled Treprostinil Dose Escalation Table**

Study Day*	Single Dose	Total Daily Dose
<b>Titration to maximum dose of 12 breaths</b>		
1-3	3 breaths QID (18 mcg)	72 mcg
4-6	4 breaths QID (24 mcg)	96 mcg
7-9	5 breaths QID (30 mcg)	120 mcg
10-12	6 breaths QID (36 mcg)	144 mcg
13-15	7 breaths QID (42 mcg)	168 mcg
16-18	8 breaths QID (48 mcg)	192 mcg
19-21	9 breaths QID (54 mcg)	216 mcg
22-24	10 breaths QID (60 mcg)	240 mcg
25-27	11 breaths QID (66 mcg)	264 mcg
28 (and beyond)	12 breaths QID (72 mcg)	288 mcg

Abbreviations: QID, 4 times daily; mcg., micrograms

\* Study day refers to the days on study drug with Day 1 referring to the first dose of study drug.

The dosing schedule is recommended as a guide only. The Investigator may determine the appropriate dosing schedule on an individual subject basis, considering tolerability and functional improvement.

If subjects are unable to tolerate the initial 3 breaths, they may decrease their next dose to 1 or 2 breaths of study drug (as determined by the Investigator) 4 times a day during waking hours. The subject will then gradually increase their dose to reach a minimum of 3 breaths, and titrate to a target dose of 9 breaths and a maximum dose of 12 breaths 4 times a day during waking hours, as clinically tolerated.

Dose changes should be conducted under appropriate medical supervision in consultation with the study site. Telephone calls/emails between the site and subject should occur prior to each dose adjustment or at least weekly to monitor for AEs, clinical worsening events, and make decisions about dose titration.

55. 6MWD data were obtained at baseline and after 8, 12, and 16 weeks.<sup>54</sup> NT-proBNP and FVC data were obtained at baseline and after 8 and 16 weeks.<sup>55</sup> Time to clinical worsening and investigator-reported exacerbations of underlying lung disease were also observed.<sup>56</sup>

56. The measurement procedures and statistical analyses to be conducted are described at a high level in section 10.3 of the final version of the INCREASE study's clinical research protocol.<sup>57</sup> The INCREASE study also had a statistical analysis plan (SAP), which provides a detailed description of the INCREASE study's statistical methodology.

57. The final version of the clinical research protocol specified that "[a] separate statistical analysis plan will document further details of the statistical methods to be employed, including any changes to planned analyses specified within this protocol. The analysis plan will be finalized prior to any unblinding of study data by the Sponsor"<sup>58</sup> and that all statistical tests were to be two-sided tests using an alpha level of 0.05. All analyses of efficacy were to be based on the intention-to-treat principle, in which all patients randomized into the study are analyzed according to the treatment group to which they were assigned by the randomization process. These specifications for the analysis are best practices for the analysis of results from a randomized clinical trial comparing an active treatment to a control. Efficacy endpoints were categorized as primary, secondary, or exploratory.

58. Safety analyses were to be conducted using all patients who received at least one dose of study drug, with analyses to be based on study drug actually received.

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<sup>54</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -792.

<sup>55</sup> *Id.*

<sup>56</sup> *Id.*

<sup>57</sup> INCREASE Protocol (UTC\_PH-ILD\_145360) at -485-487.

<sup>58</sup> *Id.* at -485.

59. A statistical analysis plan (SAP), finalized on 12 December 2019, describes in detail how each efficacy measure will be constructed from the data recorded on each patient's electronic case report form (eCRF) and the specific statistical analysis to be carried out for each efficacy measure. The SAP also details how the statistical analyses relate to study objectives, characteristics of the study design, the sequence of planned analyses, sample size considerations, the populations to be analyzed, any interim analyses to be conducted, and general considerations for data analysis.

60. The general considerations for data analysis specified in the SAP include the plan to include baseline values of efficacy variables as a covariate in individual analyses, specification of subgroups in which efficacy will be separately evaluated, plans for handling of discontinuation and missing data, and plans for treating multiple statistical comparisons.

61. The statistical analysis of each efficacy measure is discussed in detail, including primary, sensitivity, and subgroup analyses of the primary efficacy variable, change from baseline in six-minute walking distance (6MWD).

62. Measurements recorded to assess safety are outlined, as well as plans for tabulation and descriptive analyses of those measurements.

63. The INCREASE study protocol prespecified FVC (to be measured at baseline, 8 weeks, and 16 weeks) and incidence of acute exacerbation of disease as safety endpoints. The statistical analysis plan required only tabulation and descriptive statistics for these endpoints. A more detailed analysis of these endpoints was conducted.<sup>59</sup>

64. The final prespecified efficacy and safety endpoints were as follows:<sup>60</sup>

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<sup>59</sup> Nathan 2021 (UTC\_PH-ILD\_147114).

<sup>60</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -809-810.

<p><b>PRIMARY ENDPOINT</b></p> <ul style="list-style-type: none"><li>• The primary endpoint is the change in 6-minute walk distance measured at peak exposure from Baseline to Week 16.</li></ul> <p><b>SECONDARY ENDPOINTS</b></p> <ul style="list-style-type: none"><li>• The secondary efficacy endpoints are (listed in hierarchical testing order):</li><li>1. Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16</li><li>2. Time to clinical worsening calculated as the time from randomization until 1 of the following criteria are met:<ul style="list-style-type: none"><li>a. Hospitalization due to a cardiopulmonary indication</li><li>b. Decrease in 6-minute walk distance &gt;15% from Baseline directly related to disease under study, at 2 consecutive visits, and at least 24 hours apart</li><li>c. Death (all causes)</li><li>d. Lung transplantation</li></ul></li><li>3. Change in peak 6-minute walk distance from Baseline to Week 12</li><li>4. Change in trough 6-minute walk distance from Baseline to Week 15</li></ul> <p><b>EXPLORATORY ENDPOINTS</b></p> <ul style="list-style-type: none"><li>• Exploratory endpoints are (not included in hierarchical testing):</li><li>1. Change in peak 6-minute walk distance from Baseline to Week 4</li><li>2. Change in peak 6-minute walk distance from Baseline to Week 8</li><li>3. Change in quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16</li><li>4. Change in distance saturation product from Baseline to Week 16</li></ul> <p>Exploratory endpoints of optional evaluation are change in biomarkers from Baseline to Week 16, and optional evaluation of whole genome sequence. They are specified in separate documents and are not covered in the statistical analysis plan.</p> <p><b>SAFETY ENDPOINTS</b></p> <ul style="list-style-type: none"><li>• Safety endpoints are (not included in hierarchical testing):</li><li>1. Adverse events</li><li>2. Oxygenation as measured by pulse oximetry (saturation of peripheral capillary oxygenation) and supplemental oxygen requirement (L/min)</li><li>3. Pulmonary function tests, specifically: forced expiratory volume in 1 second, forced vital capacity, total lung capacity, and lung diffusion capacity</li><li>4. Clinical laboratory parameters</li><li>5. Vital signs</li><li>6. Electrocardiograms</li><li>7. Hospitalizations due to a cardiopulmonary indication</li><li>8. Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality</li></ul>
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65. Because the detailed statistical analyses of FVC and incidence of acute exacerbation of the underlying lung disease were not prespecified in the study protocol or statistical analysis plan, these analyses carried out are described as “post hoc.” Still these post hoc analyses closely followed the analytical approach that had been adopted for the prespecified efficacy variables in the INCREASE study’s statistical analysis plan. Specifically, the FVC post-

hoc analyses were carried out using the intent-to-treat population, changes from baseline were used as the assessment variable, and baseline FVC was used as a covariate. Mixed-model repeated measures analysis was used for the analysis. “Only observed data were included in the analysis; no data were imputed.”<sup>61</sup> For incidence of exacerbation of the underlying lung disease, the intent-to-treat population was also used; comparison between inhaled treprostinil and placebo was assessed using Fisher’s exact test, and time to exacerbation of the underlying lung disease was displayed using the Kaplan-Meier method and compared using the Cox proportional hazards model.<sup>62</sup>

## **b. INCREASE study results**

### **(1) 6MWD**

66. The results of the INCREASE study reported statistically significant improvements in 6MWD after 8 weeks, 12 weeks, and 16 weeks compared to baseline for PH-ILD patients treated with inhaled treprostinil. The INCREASE study results also reported improvements in 6MWD of at least 15 meters after 8 weeks, 12 weeks, and/or 16 weeks compared to baseline for PH-ILD patients treated with inhaled treprostinil.

67. The INCREASE publication indicates a statistically significant improvement in 6MWD after 16 weeks using mixed-model repeated-measures (MMRM) analysis when it reports that “[m]ixed-model repeated-measures analysis showed that the least squares mean difference between the treprostinil group and the placebo group in the change from baseline in peak 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39;  $P < 0.001$ ) (Table 2 and Fig. S1).”<sup>63</sup>

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<sup>61</sup> Nathan 2021 (UTC\_PH-ILD\_147114) at -117.

<sup>62</sup> Nathan 2021 Supplement (UTC\_PH-ILD\_112161).

<sup>63</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -793, -813. The same MMRM data for 6MWD is reported in Figure 4 of the ’327 patent.

68. The Mixed-Model Repeated Measures (MMRM) statistical methods were used to analyze treatment differences between treatments in the change in 6MWD from baseline to Week 16. The method takes into account the fact that the measurements for each patients (baseline, Week 8, Week 12, and Week 16) are correlated, and it allows for all data available for each patient to be used without the need for imputation of missing values. The specific model used, the steps taken to ensure that the model assumptions were satisfied, and the sensitivity analyses to check the robustness of the results are described in INCREASE Supplementary Appendix of Waxman (2021).<sup>64</sup> The INCREASE publication indicates a statistically significant improvement in 6MWD after 12 weeks using MMRM analysis when it reports that “[t]he least-squares mean change from baseline to week 12 in peak 6-minute walk distance was 31.29 m greater in the treprostinil group than in the placebo group ( $P < 0.001$ ).”<sup>65</sup>

69. The results of the MMRM analysis for improvements in 6MWD at 12 weeks and 16 weeks are also provided in Table 2 of the INCREASE publication:<sup>66</sup>

Table 2. Summary of Primary and Secondary End Points.*				
End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
<b>Primary end point</b>				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	-10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	-12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
† The effect of inhaled treprostinil as compared with placebo on the change in 6-minute walk distance was evaluated with the use of a mixed-model repeat measurement with the change from baseline in peak 6-minute walk distance as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; baseline 6-minute walk distance as the covariate; and subject as the random effect. Results are shown in Figures S1 and S3.				

<sup>64</sup> *Id.* at -811-812.

<sup>65</sup> *Id.* at -794, -813.

<sup>66</sup> *Id.* at -797. The same MMRM data for 6MWD is reported in Figure 4 of the '327 patent.

70. The INCREASE publication also indicates a statistically significant improvement in 6MWD after 16 weeks using the Markov chain Monte Carlo (MCMC) method when it reports that “between-group difference in the change from baseline in peak 6-minute walk distance at week 16 was significant when analyzed with multiple imputation according to the Markov chain Monte Carlo method (30.97 m; 95% CI, 16.53 to 45.41;  $P < 0.001$ ) (Fig. S3).”<sup>67</sup>

71. Like MMRM, the Markov Chain Monte Carlo method is a statistical method for estimating the difference in average change in 6MWD for inhaled treprostinil compared to placebo. The INCREASE protocol prespecified that MCMC multiple imputation would be carried out as a sensitivity analysis of the primary efficacy variable, change in 6MWD. MMRM and MCMC differ primarily in their handling of missing data.

72. The purpose of sensitivity analyses is to evaluate the robustness of findings to alternative statistical methods. When alternative statistical approaches to the same question produce similar answers—as they do in the INCREASE study—it increases confidence in the accuracy, reliability, and robustness of the results reported from the primary analysis.<sup>68</sup>

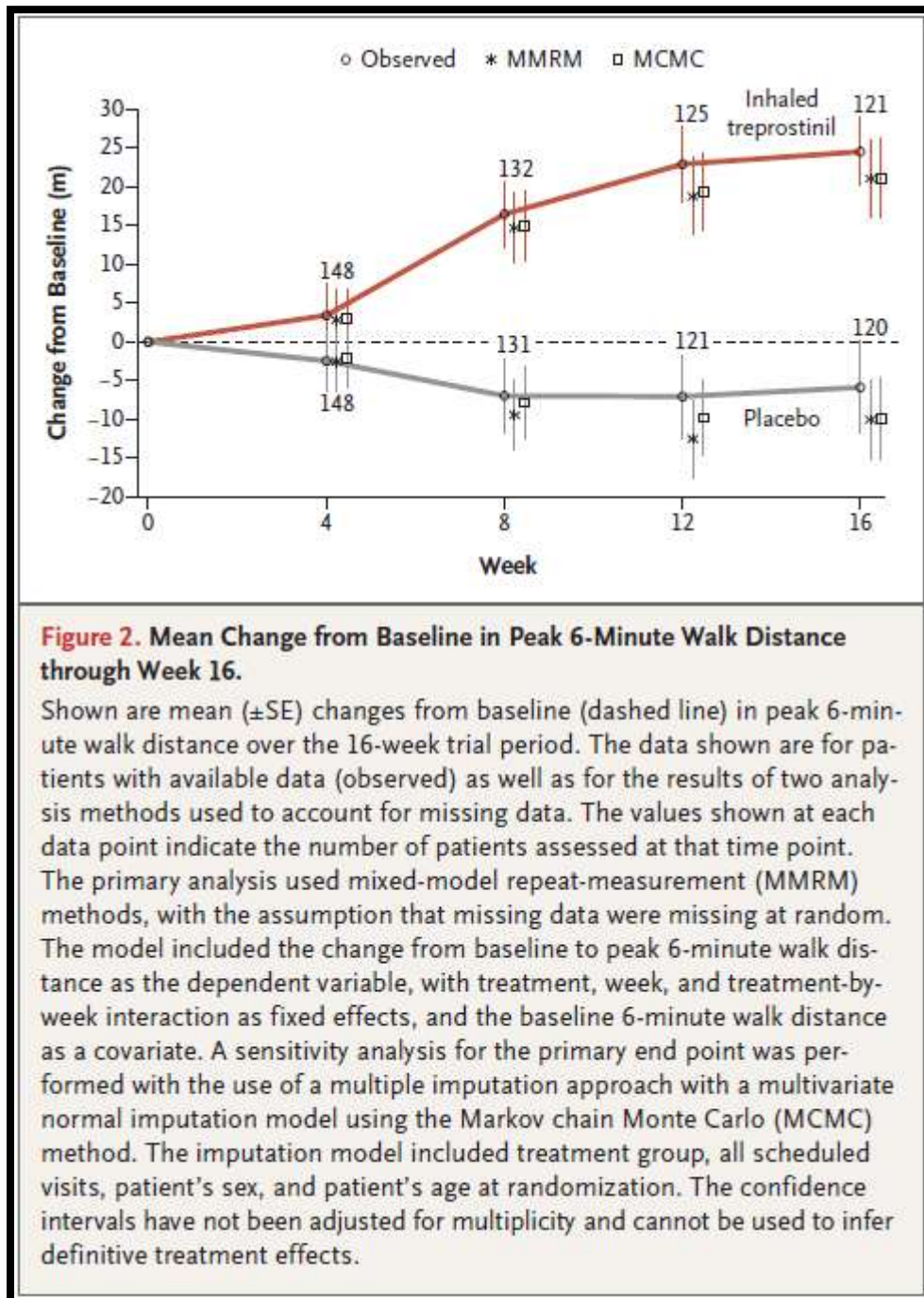
73. Figure 2 of the INCREASE publication reports MMRM and MCMC analysis for the mean change from baseline in 6MWD at 8 weeks, 12 weeks, and 16 weeks:<sup>69</sup>

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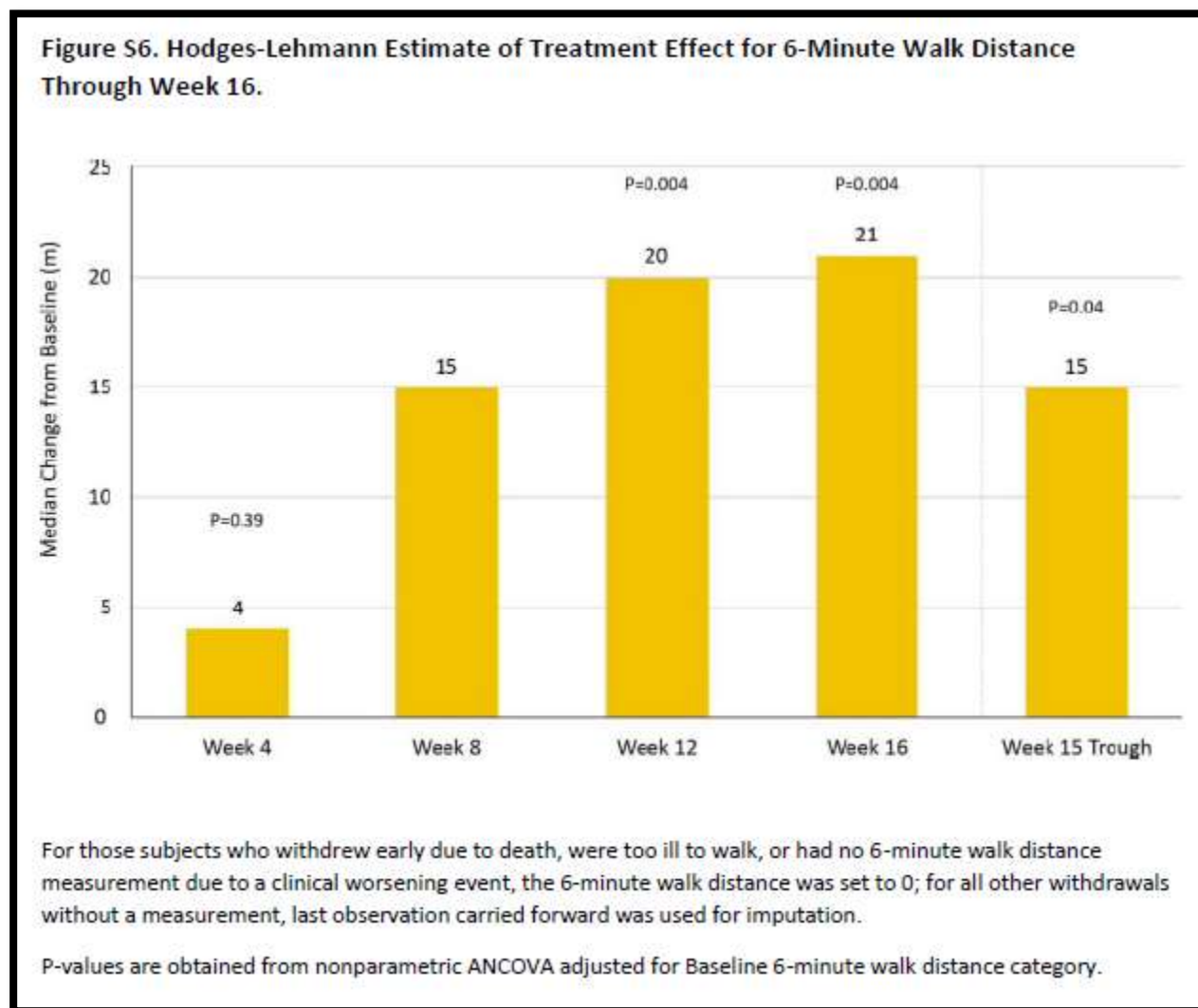
<sup>67</sup> *Id.* at -793, -815. The same MCMC data for 6MWD is reported in Figure 6 of the '327 patent.

<sup>68</sup> Thabane 2013 (UTC\_PH-ILD\_227534).

<sup>69</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -796. The same 6MWD MMRM and MCMC data is reported in Figure 3 of the '327 patent.



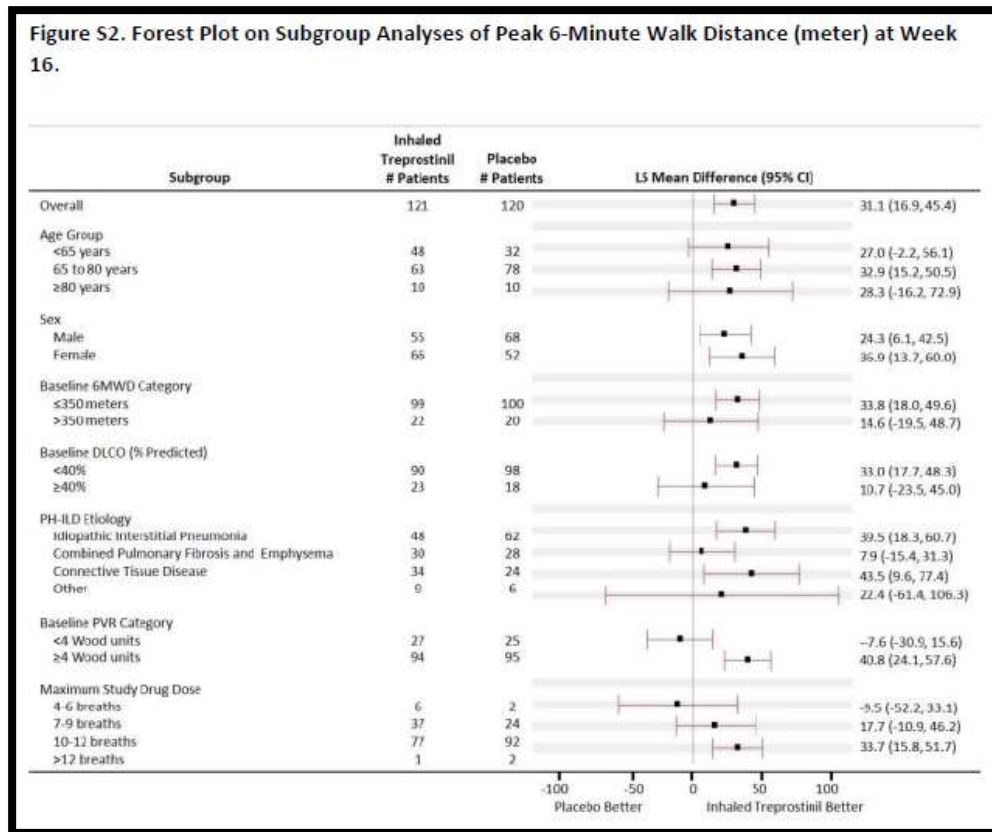
74. Figure S6 of the INCREASE publication also provides a Hodges-Lehmann estimate of treatment effect for 6MWD as 8 weeks, 12 weeks, and 16 weeks:<sup>70</sup>



75. Figure S2 of the INCREASE publication also reports subgroup data for 6MWD at week 16<sup>71</sup>:

<sup>70</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -818. The same Hodges-Lehmann estimate data for 6MWD is reported in Figure 8 of the '327 patent and Figure 3 of the Yutrepia label. Yutrepia Label (LIQ\_PH-ILD\_00126017) at -032.

<sup>71</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -814. The same 6MWD forest plot data are included in Figure 4 of the Yutrepia label. Yutrepia Label (LIQ\_PH-ILD\_00126017) at -032.



The INCREASE CSR also reports that “[s]ubjects receiving inhaled treprostinil experienced a significant improvement in peak 6MWD compared to placebo beginning at Week 8 and continuing to Week 16” and that “[t]reatment increases in peak 6MWD were observed at Week 8 (15.0 m;  $p=0.0104$ ), Week 12 (20.0 m;  $p=0.0041$ ), and Week 16 (21.0 m;  $p=0.0043$ ).”<sup>72</sup>

76. Table 11-9 of the INCREASE CSR further reports statistically significant improvements in 6MWD after 8 weeks ( $p=0.0002$ ) and 12 weeks ( $p<0.0001$ ) using MMRM analysis:<sup>73</sup>

<sup>72</sup> INCREASE CSR (UTC\_PH-ILD\_055371) at -376, *see also id.* at -432-433.

<sup>73</sup> *Id.* at -444.

**Table 11-9 Analysis of Peak 6MWD (m) Data Using Mixed Model Repeated Measurement – ITT Population**

Visit	Treatment	N	LS Mean	Estimated Difference	95% CI	p-value
Week 8	Inhaled Treprostinil	132	14.69	24.13	11.48, 36.79	0.0002
	Placebo	131	-9.45			
Week 12	Inhaled Treprostinil	125	18.77	31.29	17.37, 45.21	<0.0001
	Placebo	121	-12.52			

Abbreviations: 6MWD, 6-Minute Walk Distance; CI, confidence interval; ITT, Intent-to-Treat; LS, least square; MMRM, mixed model repeated measurement

Note: LS mean, p-values, estimated difference, and its 95% CI were from the MMRM with the change from Baseline in peak 6MWD as the dependent variable; treatment, week, and treatment by week interaction as the fixed effects; Baseline 6MWD as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

Source: Table 14.2.1.8

## (2) Plasma NT-proBNP concentrations

77. The results of the INCREASE study reported statistically significant reductions of plasma concentration of NT-proBNP after 8 weeks and 16 weeks compared to baseline for PH-ILD patients treated with inhaled treprostinil. The INCREASE study results also reported reductions in plasma concentration of NT-proBNP by at least 200 pg/ml after 8 weeks and 16 weeks compared to baseline for PH-ILD patients treated with inhaled treprostinil.

78. The INCREASE publication indicates a statistically significant reduction of plasma concentration of NT-proBNP when it reports that “[t]he NT-proBNP level decreased 15% from baseline with inhaled treprostinil and increased 46% from baseline with placebo, as assessed by the least-squares mean for the log-transformed ratio to the baseline level at week 16 (treatment ratio, 0.58; 95% CI, 0.47 to 0.72;  $P < 0.001$ ) (Fig. S4).”<sup>74</sup>

79. The statistical methods in the INCREASE study all included baseline values as covariates, recognizing the fact that patients with higher values at baseline also tend to have higher values at later time points, regardless of treatment. So the statistical analysis controls for this effect,

<sup>74</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -793-794.

ensuring that it won't interfere with assessment of the treatment effect. Least-squares means are the group means after controlling for baseline, and are expressed as the estimated group mean for individuals whose baseline is at the average baseline value.

80. Many biological measurements have highly skewed distributions, with much more variability in high values than in low values. Typically, by taking the logarithm of such values (the log-transformed data), the resulting distribution is much better described by a normal (Gaussian) bell-shaped distribution, a context in which many statistical methods work well. For this reason, the analysis of such variables is often carried out on the log-transformed data, and the results then transformed back to the original scale for purposes of description of the results.

81. These data are also reported in Table 2 of the INCREASE publication.<sup>75</sup>

Table 2. Summary of Primary and Secondary End Points.*				
End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
<b>Secondary end points§</b>				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	-396.35±1904.90	1453.95±7296.20		
Median — pg/ml	-22.65	20.65		
Range — pg/ml	-11,433.0 to 5373.1	-5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)	<0.001
§ The effect of inhaled treprostinil as compared with placebo on the change in log-transformed NT-proBNP was evaluated with the use of a mixed-model repeat measurement with the change from baseline in log-transformed NT-proBNP as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; and log-transformed baseline NT-proBNP as the covariate. Ratio to baseline is the least-squares mean of the change from baseline in log-transformed data.				
¶ The change in plasma concentration of NT-proBNP from baseline to week 16 was assessed in 156 patients in the treprostinil group and 160 in the placebo group.				
This is the treatment ratio, which is the ratio of ratios between two treatment groups.				

<sup>75</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -797. The same NT-proBNP data are reported in Table 5 of the '327 patent.

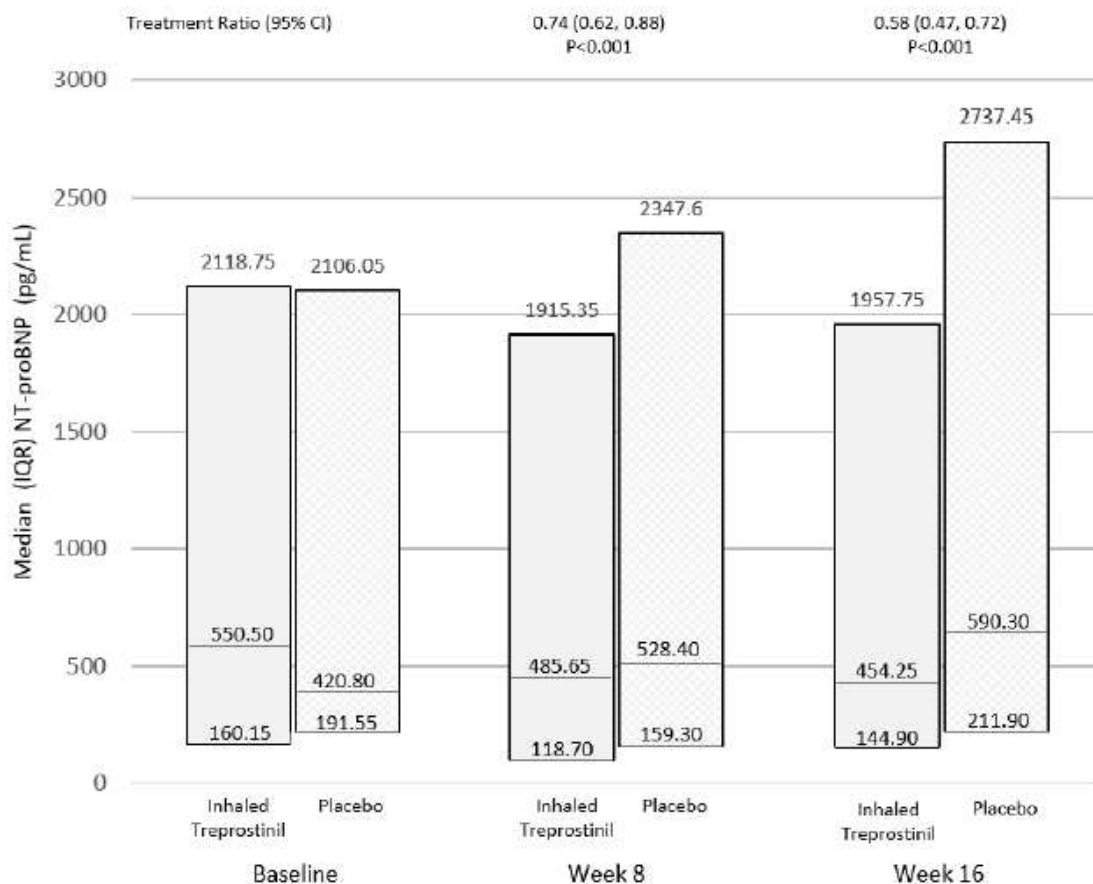
As shown above, Table 2 of the INCREASE publication also reports that the mean change in NT-proBNP levels from baseline after 16 weeks for the inhaled treprostinil group was -396.35 pg/ml while the mean change in NT-proBNP levels from baseline after 16 weeks for the placebo group was 1453.95 pg/ml.

82. The same 16 week NT-proBNP data regarding treatment ratio are provided in Figure S4 of the INCREASE publication along with 8 week NT-proBNP data:<sup>76</sup>

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<sup>76</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -816.

**Figure S4. NT-proBNP Results by Study Visit (pg/mL).**



CI, confidence interval; IQR, interquartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide

As displayed above, inhaled treprostinil was associated with a 42% reduction in NT-proBNP compared to placebo at Week 16 (Treatment Ratio 0.58; 95% CI: 0.47, 0.72; P<0.001). Only subjects with a Baseline NT-proBNP measurement are included in this analysis. P-values, estimated treatment ratio, and associated 95% CIs (LS Mean difference expressed as ratio) are obtained from the analysis of covariance with change from baseline in log-transformed data in NT-proBNP as the dependent variable, treatment as the fixed effect, and log-transformed baseline NT-proBNP as a covariate. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

83. Table 11-6 of the INCREASE Clinical Study Report includes the same statistically significant NT-proBNP reduction data at week 8 and week 16:<sup>77</sup>

<sup>77</sup> INCREASE CSR (UTC\_PH-ILD\_055371) at -438.

**Table 11-6 Analysis of NT-proBNP (pg/mL) Data Using Mixed Model Repeated Measurement – ITT Population**

Visit	Treatment	N	LS Mean	Contrast	Estimated Difference	95% CI	p-value
Week 8	Inhaled Treprostinil	145	0.82	Inhaled Treprostinil - Placebo	0.74	0.62, 0.88	0.0007
	Placebo	140	1.12				
Week 16	Inhaled Treprostinil	123	0.85	Inhaled Treprostinil - Placebo	0.58	0.47, 0.72	<0.0001
	Placebo	127	1.46				

Abbreviations: CI, confidence interval; ITT, Intent-to-Treat; LS, least square; MMRM, mixed model repeated measurement; NT-proBNP, N-terminal pro-brain natriuretic peptide

Note: LS mean, p-values, estimated difference, and associated 95% CI were from the MMRM with the change from Baseline in log-transformed NT-proBNP as the dependent variable; treatment, week, and treatment by week interaction as the fixed effects; and log-transformed Baseline NT-proBNP as the covariate. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

Source: Table 14.2.2.5

84. Table 11-5 of the INCREASE Clinical Study Report also reports statistically significant ( $p=0.0005$ ) NT-proBNP data at Week 8<sup>78</sup> using ANCOVA and LOCF imputation<sup>79</sup>:

**Table 11-5 Summary and Analysis of NT-proBNP (pg/mL) Data – ITT Population**

Visit and Statistics	Inhaled Treprostinil N=163		Placebo N=163		p-value*
	Value	Change from Baseline	Value	Change from Baseline	
<b>Week 8</b>					
n	156	156	160	160	–
Mean (SD)	1376.72 (2099.32)	-480.81 (1659.28)	2412.91 (4841.95)	604.05 (3220.46)	–
Geometric mean (geometric SD)	481.00 (4.86)	–	601.23 (5.71)	–	–
Median	485.65	-11.25	528.40	0.00	–
Interquartile	118.70, 1915.35	-469.95, 42.40	159.30, 2347.60	-52.33, 317.40	–
Min, Max	10.2, 13,797.0	-9704.2, 3757.0	10.2, 40,511.0	-5483.3, 34,807.3	–
LS mean (SE)	–	0.8319 (1.05862)	–	1.1027 (1.05786)	0.0005
LS mean difference (SE)	–	0.7545 (1.08336)	–	–	–
95% CI of LS mean difference	–	(0.6445, 0.8832)	–	–	–

As shown above, Table 11-5 of the INCREASE Clinical Study Report also reports that the mean change in NT-proBNP levels from baseline after 8 weeks for the inhaled treprostinil group was -480.81 pg/ml while the mean change in NT-proBNP levels from baseline after 8 weeks for the placebo group was 604.05 pg/ml.

<sup>78</sup> INCREASE CSR (UTC\_PH-ILD\_055371) at -437.

<sup>79</sup> INCREASE CSR (UTC\_PH-ILD\_055371) at -436.

### (3) Clinical worsening events

85. The results of the INCREASE study reported statistically significant reductions of clinical worsening events due to ILD including hospitalization for cardio-pulmonary indication or to decrease in 6MWD by more than 15% compared to baseline or to death or to lung transplantation.

86. The INCREASE publication indicated a statistically significant reduction of clinical worsening events due to ILD using a log-rank test when it reported that “[c]linical worsening occurred in 37 patients (22.7%) in the treprostinil group, as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P = 0.04 by the log-rank test) (Fig. S5).”<sup>80</sup>

87. The same data is also reported in Table 2 of the INCREASE publication which also includes a further breakdown of the types of clinical worsening events:<sup>81</sup>

Table 2. Summary of Primary and Secondary End Points.*				
End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		

\* Plus-minus values are means ±SE, unless otherwise indicated. For secondary end points, the confidence intervals (CIs) have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. NT-proBNP denotes N-terminal pro-B-type natriuretic peptide.

\*\* This is a hazard ratio, calculated from a Cox proportional-hazards model. The P value was calculated with the use of a log-rank test stratified by the baseline 6-minute walk distance category.

<sup>80</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -794.

<sup>81</sup> *Id.* at -797. The same clinical worsening event data are also included in Table 3 (and the immediately preceding text) of the Yutrepia label. Yutrepia Label (LIQ\_PH-ILD\_00126017) at -032-033.

88. The data reported in Table 2 of the INCREASE publication also indicate that 31 of 163 patients treated with inhaled treprostinil and 50 of 163 patients treated with placebo experienced at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared to a baseline 6-minute walk distance prior to administration of the study treatment. This difference is statistically significant ( $p=0.021$ , by Fisher's exact test).<sup>82</sup>

89. The INCREASE publication also reported the data relating to clinical worsening events in a Kaplan-Meier plot.<sup>83</sup>

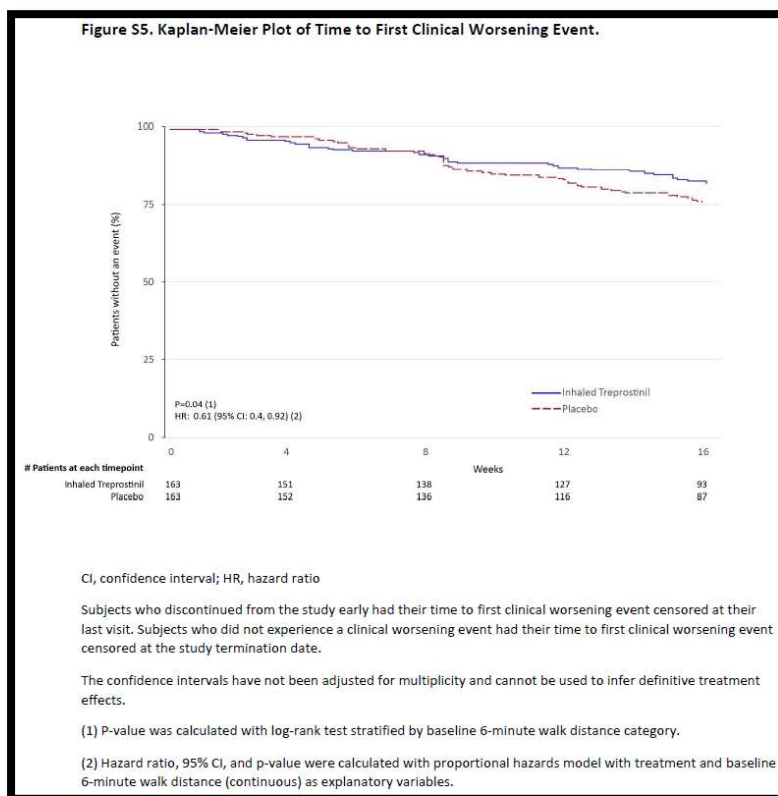
<sup>82</sup> Calculation of Fisher Exact Test using Stata version 18.5:

```
. // Clinical worsening: hospitalization and/or 6MWD decrease of >15%
. tabi 31 132 \ 50 113, exact
```

	col		
row	1	2	Total
1	31	132	163
2	50	113	163
Total	81	245	326

```
Fisher's exact = 0.021
1-sided Fisher's exact = 0.010
```

<sup>83</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -817. The same Kaplan-Meier plot of time to first clinical worsening event is reported in Figure 1 of the '327 patent and Figure 5 of the Yutrepia label. Yutrepia Label (LIQ\_PH-ILD\_00126017) at -033.



#### (4) Exacerbations due to ILD

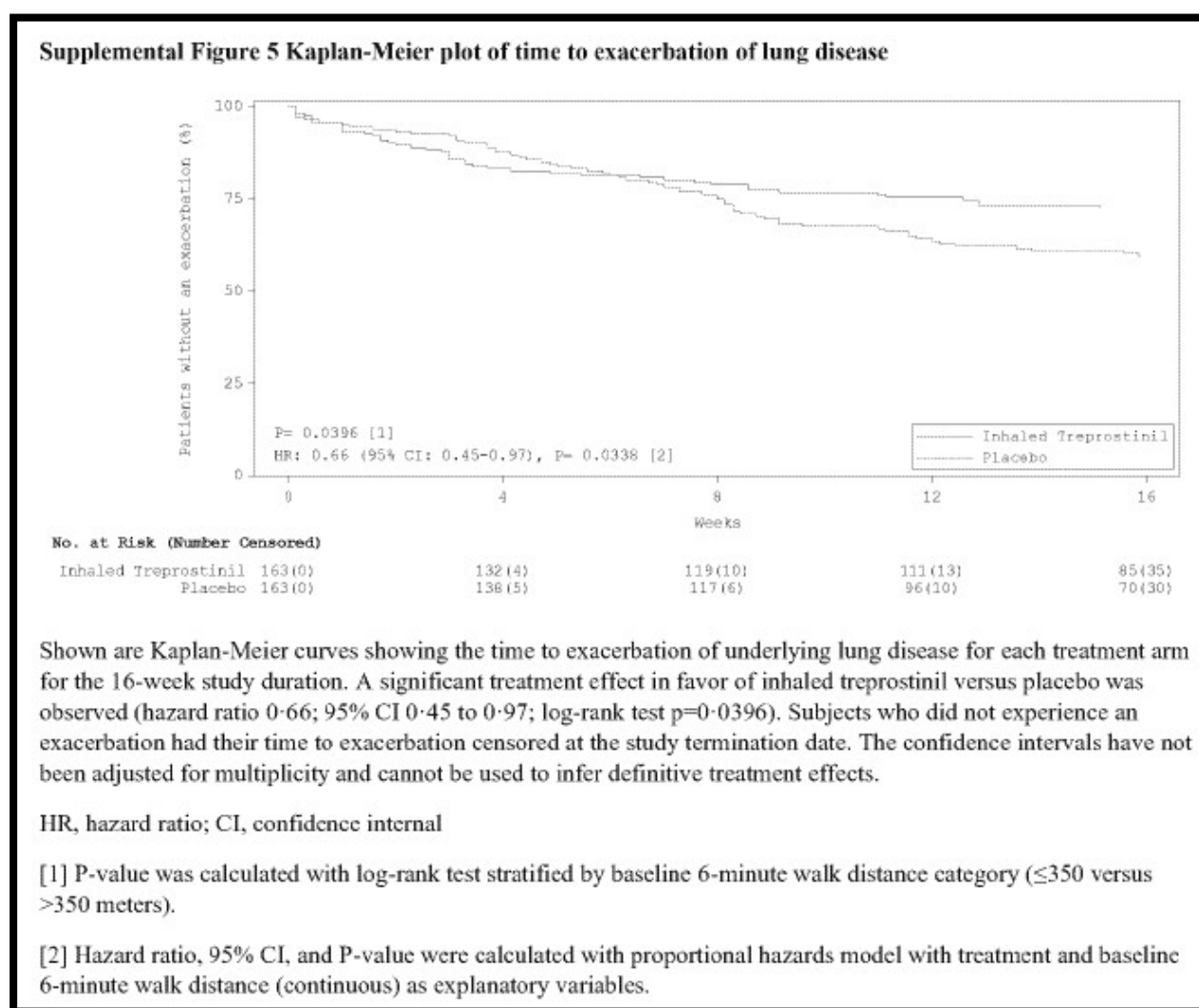
90. The results of the INCREASE study reported statistically significant reductions of exacerbations of ILD.

91. The INCREASE publication indicated a statistically significant reduction in exacerbations of ILD using a Fisher's exact test when it reported that "[s]ignificantly fewer patients in the treprostinil group than in the placebo group had exacerbations of underlying lung disease (43 [26.4%] vs. 63 [38.7%]; P = 0.02 by Fisher's exact test)."<sup>84</sup>

92. Fisher's exact test is a standard method for assessing the statistical significance of differences between counts of an outcome in one group as compared to counts of the same outcome in a comparison group, where each subject experiences the outcome either once or not at all.

<sup>84</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -796. The same information is reported in the '327 patent. '327 patent (UTC\_PH-ILD\_005310) at 35:25-28.

93. A post-hoc analysis of the INCREASE study reports the same conclusion regarding the statistical significance of the exacerbation data<sup>85</sup> and further includes a Kaplan-Meier plot of time to exacerbation of lung disease indicating “[a] significant treatment effect in favor of inhaled treprostinil versus placebo”:<sup>86</sup>



<sup>85</sup> Nathan 2021 (UTC\_PH-ILD\_147114) at -119 (“43 (26%) of 163 patients in the treatment group had an exacerbation of underlying lung disease compared with 63 (39%) of 163 patients in the placebo group ( $p=0.02$  by Fisher's exact test”).

<sup>86</sup> Nathan 2021 Supplement (UTC\_PH-ILD\_112161) at -169.

94. The Kaplan-Meier curve is a widely-used statistical method used to show how the fraction of individuals who have not (yet) experienced a particular event (such as an exacerbation of ILD) varies as a function of time since initiation of treatment. Such figures are also called “survival curves.” Roughly speaking, the curve shows the probability over time of surviving without experiencing the event. The method correctly takes account of all information available from each individual in the case that some individuals have incomplete information.

95. The log-rank test is a statistical method for assessing whether two survival curves differ.

96. The hazard ratio is a measure comparing two survival curves. As defined by the National Cancer Institute, the hazard ratio is:

A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one or less than one means that survival was better in one of the groups.<sup>87</sup>

97. The INCREASE CSR also reports that “[t]he reduction in exacerbations in the inhaled treprostinil group was statistically significant using a Chi-square test ( $p=0.0180$ ), representing a 34% reduction in risk.”<sup>88</sup>

98. The chi-square(d) test is an alternative to the Fisher’s exact test for assessing the difference between two groups in the fraction of individuals experiencing an event. When the total number of events observed is quite small, the p-value calculated using the chi-squared method can

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<sup>87</sup> National Cancer Institute 2025. <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/hazard-ratio>, accessed 10 February 2025 (UTC\_PH-ILD\_227452).

<sup>88</sup> INCREASE CSR (UTC\_PH-ILD\_055371) at -469.

be unreliable, so in that case many statistics texts recommend the Fisher test. However, when the number of events is modest (say more than 10), the results from the two tests are generally in close agreement. For example, in the case of exacerbation rates cited above, the p-value from the chi-square test is  $p=0.018$  and the p-value from Fisher's exact test is 0.024.

**(5) Forced vital capacity**

99. The results of the INCREASE study reported statistically significant improvements in FVC after 8 weeks and 16 weeks compared to baseline for PH-ILD patients treated with inhaled treprostinil. The INCREASE study results also reported improvements in FVC of at least 20 ml after 8 weeks and 16 weeks compared to baseline for PH-ILD patients treated with inhaled treprostinil.

100. The INCREASE publication indicates a statistically significant improvement in % predicted FVC using MMRM analysis after 8 weeks ( $p=0.01$ ) and 16 weeks ( $p=0.03$ ) in Table S6:<sup>89</sup>

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<sup>89</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -825. The same FVC MMRM data are reported in Table 1 of the '327 patent.

**Table S6. Analysis of Lung Function Test Parameters Using Mixed Model Repeated Measurement.**

Variable	Contrast: Inhaled treprostinil - Placebo			
Visit			Estimated Difference	
Treatment	N	LS Mean	(95% CI)	P-value
FVC (mL)				
Week 8				
Inhaled treprostinil	142	5.49	28.47	0.35
Placebo	141	-22.98	(-30.81, 87.74)	
Week 16				
Inhaled treprostinil	130	9.77	44.40	0.21
Placebo	126	-34.63	(-25.25, 114.05)	
FVC (% predicted)				
Week 8				
Inhaled treprostinil	142	0.77	1.79	0.01
Placebo	141	-1.02	(0.37, 3.21)	
Week 16				
Inhaled treprostinil	130	1.07	1.80	0.03
Placebo	126	-0.72	(0.20, 3.39)	

101. A post-hoc analysis of the INCREASE study indicated a statistically significant improvement in absolute FVC for the idiopathic interstitial pneumonia (IIP) subpopulation after 16 weeks using MMRM when it reported that “[a] subgroup analysis of patients with idiopathic interstitial pneumonia showed significant FVC differences at week 16 (108.2 mL; SE 46.9; 95% CI 15.3 to 201.1; p=0.023).”<sup>90</sup>

102. A post-hoc analysis of the INCREASE study indicated a statistically significant improvement in absolute FVC for the idiopathic pulmonary fibrosis (IPF) subpopulation after 16 weeks using MMRM when it reported that “analysis of patients with idiopathic pulmonary fibrosis

<sup>90</sup> Nathan 2021 (UTC\_PH-ILD\_147114) at -118. The same FVC MMRM analysis for the IIP subgroup is reported in Table 2 of the ’327 patent.

showed... significant [FVC] differences of 168.5 mL (64.5; 40.1 to 297.0;  $p=0.011$ ) at week 16 (figure 3A).”<sup>91</sup>

103. The INCREASE post hoc analysis also reported statistically significant treatment effects with respect to % predicted FVC in the IIP and IPF subpopulations after 8 and 16 weeks. Regarding the IIP subpopulation, the resulting analysis reported a p-value of  $p=0.037$  after 8 weeks and  $p=0.0096$  after 16 weeks.<sup>92</sup> Regarding the IPF subpopulation, the resulting analysis reported a p-value of  $p=0.038$  after 8 weeks and  $p=0.015$  after 16 weeks.<sup>93</sup>

### **c. Impact of INCREASE results**

104. In contrast to the under-sampled, nonrandomized, noncomparative, uncontrolled, single-arm, single-center studies on which Dr. Channick relies in his Opening Report—Saggar 2014, Parikh 2016, Agarwal 2015, and Faria-Urbina 2018 (the “Uncontrolled Studies”)—the INCREASE study was a large, well-designed, and well-executed prospective, comparative, multicenter, randomized (1:1 inhaled treprostinil:placebo), double-blinded, placebo-controlled clinical trial in which inhaled treprostinil treatment was compared to placebo treatment in 326 PH-ILD patients over 16 weeks.

105. I have also exhaustively detailed (in my Rebuttal Report) how the mere fact that the Uncontrolled Studies lack meaningful controls prevents the Uncontrolled Studies from demonstrating an inhaled treprostinil treatment effect in PH-ILD patients.<sup>94</sup> By contrast, the INCREASE study’s randomized placebo-controlled design permits the identification of inhaled

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<sup>91</sup> Nathan 2021 (UTC\_PH-ILD\_147114) at -118-119. The same FVC MMRM analysis for the IPF subgroup is reported in Table 3 of the ’327 patent.

<sup>92</sup> Nathan 2021 (UTC\_PH-ILD\_147114) at -118. The same FVC MMRM analysis for the IIP subgroup is reported in Table 2 of the ’327 patent.

<sup>93</sup> Nathan 2021 (UTC\_PH-ILD\_147114) at -118-119. The same FVC MMRM analysis for the IPF subgroup is reported in Table 3 of the ’327 patent.

<sup>94</sup> Thisted Reb. Rpt. §§ VII, IX.B-E, XI, XV.

treprostinil treatment effects in PH-ILD patients, for the reasons I detail above and in my Rebuttal Report.<sup>95</sup> Moreover, the INCREASE Study's randomized placebo-controlled design and well-sampled, prospective, multi-center, and double-blinded characteristics eliminate multiple sources of bias that I identified in my Rebuttal Report that apply to the Uncontrolled Studies.<sup>96</sup> As detailed in my Rebuttal Report, these biases render the Uncontrolled Studies' overstated and lacking generalizability and reliability.<sup>97</sup>

106. I note that the INCREASE study incorporated the following features that the Uncontrolled Studies lack:

- a. The INCREASE study had a large sample size. 326 patients underwent randomization, and 130 and 128 patients who were respectively assigned to the treatment and placebo arms completed the week 16. The INCREASE study's large sample size i) ensured that the INCREASE study was adequately powered to detect clinically important differences in effects on exercise capacity and ii) provided a large base of patients to represent the population of PH-ILD patients.
- b. The INCREASE study specified patient inclusion and exclusion criteria in advance of patient recruitment, ensuring a well-defined patient population prior to randomization.
- c. The INCREASE study included a placebo control arm against which efficacy of inhaled treprostinil in the treatment arm could be assessed.

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<sup>95</sup> Thisted Reb. Rpt. §§ X, XI.

<sup>96</sup> Thisted Reb. Rpt. §§ IX.B-E, X, XI.

<sup>97</sup> Thisted Reb. Rpt. §§ IX.B-E, XI, XV.

- d. The INCREASE study defined the primary, secondary, and exploratory efficacy and safety endpoints, defined a schedule of visits at which each was assessed in every patient, and defined clear protocols for conducting each assessment. This ensured that data were collected in a consistent manner, maximizing data quality and interpretability of results.
- e. The INCREASE study randomized allocation of treatment (inhaled treprostinil or placebo), ensuring that no factor other than treatment assignment could systematically affect the measured effects of each treatment arm.
- f. The INCREASE study blinded all parties—patients, investigators, steering committee, and sponsors—ensuring that assessments could not be influenced, consciously or unconsciously, by knowledge of the treatment to which each patient was assigned.
- g. The INCREASE study established a well-defined plan for statistical analysis of the data, and that plan was finalized before any data were unblinded.
- h. The INCREASE study’s analyses compare the changes between inhaled treprostinil and placebo treatment arms, thereby ensuring that any possible effects of regression to the mean would be present in both treatment groups and so would cancel out in any statistical comparison.
- i. The INCREASE study’s statistical methods fully account for all randomized patients, not just those whose disease did not worsen, or who died, or who required lung transplantation. For example, the INCREASE

study's protocol specifically describes that patients whose 6MWD could not be obtained due to inability to perform the test, death, or lung transplantation would be recorded as having a 0 meter 6MWD; and any patient whose 6MWD was missing for any other reason (such as patient deciding not to continue with the study) would have the most recent 6MWD entered (this is known as the "last observation carried forward" (LOCF) method of imputing missing values). This ensured that adverse *post hoc* selection due to patient status would not affect the assessment of the INCREASE study's outcomes.

- j. The INCREASE study included planned sensitivity analyses to examine the effects of different statistical assumptions concerning missing data (MMRM and MCMC) and to verify that the INCREASE study's findings did not depend on a particular method of analysis.
- k. The INCREASE study was conducted at 93 geographically scattered study centers, ensuring wide generalizability of INCREASE study's results.

107. As noted in detail in my Rebuttal Report, none of the Uncontrolled Studies were capable of identifying treatment effects of inhaled treprostinil in PH-ILD patients.<sup>98</sup> In contrast to the Uncontrolled Studies, the INCREASE study randomized a well-defined cohort of PH-ILD patients; carefully monitored outcomes and obtained data in a well-defined, blinded, and uniform way over a scheduled and fixed period of treatment; and rigorously compared outcomes in patients treated with inhaled treprostinil to those receiving placebo treatment. Therefore, the INCREASE

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<sup>98</sup> Thisted Reb. Rpt. §§ IX.B-E, XI, XV.

study was the first study that was capable of identifying whether inhaled treprostinil was an effective and safe treatment in PH-ILD patients.

108. However, the INCREASE study's findings were not a foregone conclusion. The Uncontrolled Studies that involved inhaled treprostinil all concerned mixed groups of pulmonary hypertension patients that included WHO Group 3 PH, e.g., these sample populations contained PH-ILD, PH-CPFE, and PH-COPD patients. For example, the Agarwal 2015 authors concluded that "Group 3 PH can be effectively and safely treated with [inhaled treprostinil]," making no distinction between PH-COPD and PH-ILD patients. The chart review reported in Faria-Urbina 2018 was similar in this regard. In fact, both Agarwal 2015 and Faria-Urbina 2018 report data suggesting that PH-COPD patients appeared to fare better on inhaled treprostinil than PH-ILD patients. The authors of Faria-Urbina 2018 even emphasized that "COPD patients tended to have greater benefit from iTre treatment . . . ." <sup>99</sup> However, if either of Agarwal 2015 or Faria-Urbina 2018 were truly predictive of the results that would be obtained in a properly conducted prospective randomized clinical trial (that is, the "prospective clinical trial" and "larger prospective studies" the authors respectively called for), one would predict that inhaled treprostinil would be more effective in PH-COPD than PH-ILD, if it was effective at all in the latter. That was not the case, as detailed in my Rebuttal Report. <sup>100</sup> The prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial of inhaled treprostinil in PH-COPD—the PERFECT trial—which enrolled 188 subjects, yielded no evidence of effectiveness for inhaled treprostinil, and demonstrated more serious adverse events, deaths, and treatment discontinuations than placebo—leading to the study's termination.

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<sup>99</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -941.

<sup>100</sup> Thisted Reb. Rpt. §§ IX.B-E, X, XI.

109. With the INCREASE study completed, its findings demonstrate the outcomes that can be expected when patients with PH-ILD are administered inhaled treprostinil for multiple weeks. Unlike the single-center studies that comprise the Uncontrolled Studies, the INCREASE study findings informing efficacy and safety are pooled from 93 study centers spread throughout the United States. This indicates that the INCREASE study's findings are not driven by data generated from one, two, or even a handful of specialty centers but instead typify results from a broad range of clinical settings as well as patient demographics.

110. With the INCREASE study completed, its findings also demonstrate that administering Tyvaso to PH-ILD patients in a manner consistent with the dosing regimen used in INCREASE provides the statistically significant treatment effects that I detailed above. Therefore, PH-ILD patients administered Tyvaso in this manner, would be more likely than not to exhibit treprostinil treatment effects consistent with those I detail above.

111. Likewise, I note that the INCREASE study's findings inform the efficacy and safety of other inhaled products with treprostinil as their only active ingredient. If such a product administers treprostinil to PH-ILD patients in an amount consistent with the amounts delivered in the INCREASE study, and if administering that product provides comparable bioavailability, I would expect that product to produce efficacy results consistent with those I detail above, provided that the product did not introduce additional safety or tolerability issues not present with Tyvaso. In fact, as described above, this is the principle behind FDA permitting product sponsors to rely on FDA's clinical efficacy and safety findings of the sponsor-selected RLD if the product sponsors establish the requisite biocomparability or bioequivalence of their product with respect to the RLD.<sup>101</sup>

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<sup>101</sup> *Supra* Section III.C.

112. I also note that inhaled products comprising treprostinil as their only active ingredient and that exhibit comparable bioavailability, safety, and tolerability to Tyvaso, and that are administered consistent with the INCREASE study dosing regimen, would be expected to replicate the INCREASE study's prespecified efficacy and safety endpoints. I would also expect that endpoints which were examined after unblinding but not prespecified in the study protocol would be more likely than not to be replicated. This would be true whether or not a particular endpoint was included among those listed on those products' labels.

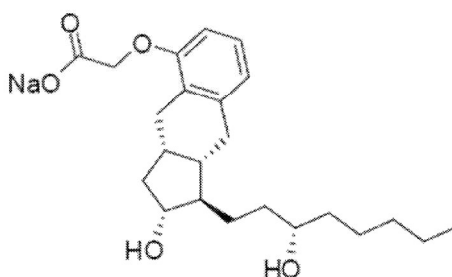
#### IV. LIQUIDIA'S ACCUSED YUTREPIA PRODUCT

##### A. Liquidia's Yutrepia product indicated for PH-ILD to improve exercise ability.

##### 1. Liquidia's Yutrepia product

113. Liquidia's Yutrepia product is an inhalable dry powder that—like Tyvaso and Tyvaso DPI—uses treprostinil as the active ingredient.<sup>102</sup> Yutrepia uses a sodium salt of treprostinil.<sup>103</sup>

YUTREPIA contains treprostinil sodium, a prostacyclin mimetic. The chemical name for tresprostnil sodium is 2-([(1R,2R,3aS,9aS)-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H,2H,3H,3aH,4H,9H,9aH-cyclopenta[b]naphthalen-5-yl]oxy}acetic acid, sodium salt with the structural formula:



<sup>102</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020, -022, -026-027, -034, -036-054; compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020, -026 with 2022 Tyvaso Label (UTC\_PH-ILD\_005268) at -268, -274 and 2022 Tyvaso DPI Label (UTC\_PH-ILD\_010709) at -709, -715-716; see *supra* § III.D.1.

<sup>103</sup> See Yutrepia Label (LIQ\_PH-ILD\_00126017) at -026.

Liquidia elected to pursue the 505(b)(2) approval pathway for its Yutrepia product as detailed below and has been tentatively approved for the PAH and PH-ILD indications:<sup>104</sup>

**-----INDICATIONS AND USAGE-----**

YUTREPIA is a prostacyclin mimetic indicated for the treatment of:

- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). (1.1)
- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%). (1.2)

114. Yutrepia further consists of the following inactive ingredients: L-leucine, polysorbate 80, sodium citrate, sodium chloride, and trehalose.<sup>105</sup> Every 5mg of Yutrepia consists of 28µg of treprostinil sodium salt, which is equivalent to 26.5µg of treprostinil. Yutrepia's tentatively approved label, instructions for use, and packaging confirm that Yutrepia "should only be delivered using the capsule-based inhaler."<sup>106</sup> Yutrepia's tentatively approved label and instructions for use describe and illustrate this dry powder inhaler.<sup>107</sup>

115. The Yutrepia label, instructions for use, and packaging indicates that capsules will come in the following four strengths:<sup>108</sup>

<sup>104</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -017-021, -055; *infra* § IV.A.2.

<sup>105</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -026.

<sup>106</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -026-027, -034, -036-054.

<sup>107</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021, -034, -036-046.

<sup>108</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020, -022, -027, -034, -036, -048-054.

Table 4: YUTREPIA Carton Contents by Capsule Strength		
Capsule Strength (mcg treprostinil)	Capsule Description	NDC Number
26.5	Opaque yellow cap, clear body, imprinted with "LIQUIDIA 26.5" in black ink radially on cap	72964-011-01
53	Opaque green cap, clear body, imprinted with "LIQUIDIA 53" in white ink radially on cap	72964-012-01
79.5	Opaque blue cap, clear body, imprinted with "LIQUIDIA 79.5" in white ink radially on cap	72964-013-01
106	Opaque purple cap, clear body, imprinted with "LIQUIDIA 106" in white ink radially on cap	72964-014-01

Yutrepia's tentatively approved label and instructions for use instruct patients to take two breaths per capsule, and the second breath ensures that the patient receives the full dose that a particular capsule strength provides.<sup>109</sup> Yutrepia's tentatively approved label nonetheless indicates that the four capsule strengths do not deliver the entire amount of active ingredient available within a capsule, providing *in vitro* data estimating the dose of treprostinil delivered from each of the available capsule strengths:<sup>110</sup>

YUTREPIA Inhalation Powder Delivered Dose	
Capsule Strength (treprostinil)	Dose Delivered <sup>a</sup>
26.5 mcg	15.1 mcg
53 mcg	36.0 mcg
79.5 mcg	56.6 mcg
106 mcg	75.7 mcg
<sup>a</sup> Amount of treprostinil delivered from the device mouthpiece under an <i>in vitro</i> flow rate of 99 L/min with a collection time of 1.2 seconds (2 L total volume).	

<sup>109</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021, -042-043; *see also* Product Dossier (LIQ\_PH-ILD\_00146984) at -6999-7000.

<sup>110</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at 027; *infra* § IV.A.2.b.

As noted in the table, the smallest amount of treprostinil delivered from a capsule for patients administered Yutrepia will be approximately 15.1 mcg.<sup>111</sup>

116. The tentatively approved Yutrepia label instructs how to administer Yutrepia in terms of Tyvaso breaths.<sup>112</sup> Table 1 of the Yutrepia label correlates Tyvaso dosing with Yutrepia dosing:<sup>113</sup>

Table 1: YUTREPIA Dosing in Patients Transitioning from Treprostinil Inhalation Solution	
Current Tyvaso Dose*	YUTREPIA Dose
Breaths	mcg
≤5	26.5
≥6 and ≤8	53
≥9 and ≤11	79.5
≥12 and ≤14	106
≥15 and ≤17	132.5
≥18	159

\*Each breath of Tyvaso delivers approximately 6 mcg of treprostinil

117. The tentatively approved Yutrepia label instructs treprostinil-naïve patients to “begin with 26.5 mcg [of Yutrepia] 3 to 5 times per day, in 2 breaths.”<sup>114</sup> This dosing, when converted to delivered dosage, is nearly identical to the recommended initial dose in the INCREASE study.<sup>115</sup> This delivered dose also corresponds to the initial dosage on the Tyvaso and Tyvaso DPI labels.<sup>116</sup> The tentatively approved Yutrepia label further instructs those transitioning

<sup>111</sup> Yutrepia Label at LIQ\_PH-ILD\_00126027.

<sup>112</sup> Yutrepia Label at LIQ\_PH-ILD\_00126021-00126022; *infra* § IV.A.2.b.

<sup>113</sup> Yutrepia Label at LIQ\_PH-ILD\_00126021-00126022; *infra* § IV.A.2.b.

<sup>114</sup> Yutrepia Label at LIQ\_PH-ILD\_00126021.

<sup>115</sup> Compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022, -027 with INCREASE Protocol (UTC\_PH-ILD\_145360) at -470-471; *supra* § III.D.2.a; *infra* § IV.A.2.b.

<sup>116</sup> Compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022, -027 with 2022 Tyvaso Label (UTC\_PH-ILD\_005268) at -269 and 2022 Tyvaso DPI Label (UTC\_PH-ILD\_010709) at -710-711; *see also* Rajeev Saggat Dep. Tr. at 90:11-22 (Q. What’s the starting dose of Yutrepia? A. 26.5 micrograms. A. I said 26.5 micrograms. Q. And both Tyvaso and Tyvaso DPI can offer doses of -- similar doses of treprostinil, correct? A. Yes, similar doses. That is correct. Q. And both Tyvaso and Tyvaso DPI doses and Yutrepia doses can be increased above 26.5 micrograms per administration, correct? A. Yes, that is correct.); *infra* § IV.A.2.bb.

from the Tyvaso inhalation solution to follow the conversion table reproduced just above at “3 to 5 times per day,” i.e., corresponding to Tyvaso’s QID instructions, and “in 2 breaths.”<sup>117</sup> Accordingly, the tentatively approved Yutrepia label instructs that both treprostinil-naïve patients and patients transitioning from Tyvaso take 2 breaths per treatment session, i.e., per capsule, and thus a single administration event does not exceed 15 breaths by the patient.<sup>118</sup> Yet, as noted above, the tentatively approved label and instructions for use provide this two-breath-per-capsule instruction to ensure that patients completely inhale a capsule’s contents.<sup>119</sup>

118. The tentatively approved Yutrepia label instructs that “dose increases of 26.5 mcg per dose each week may be implemented, as tolerated[,]” for all patients and that the “target maintenance dosage is 79.5-106 mcg, 4 times daily.”<sup>120</sup> When these doses are converted to delivered dosages, again, they align with the dosing regimen used in the INCREASE study.<sup>121</sup> Likewise the delivered dose amounts correspond to dosages on the Tyvaso and Tyvaso DPI labels.<sup>122</sup> Accordingly, the tentatively approved Yutrepia label instructs targeting administering a single inhalation event with a delivered dose of 15-100 µg of treprostinil or a pharmaceutically acceptable salt thereof.<sup>123</sup> Yet the tentatively approved Yutrepia label acknowledges greater doses

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<sup>117</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021.

<sup>118</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021.

<sup>119</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021, -042-043.

<sup>120</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -022; Rajeev Saggar Dep. Tr. 220:6-15 (A. Well, we have – we’re a capsule-based formulation, so our -- we are titrated based on 26.5-microgram increments. Tyvaso is titrated on-- Tyvaso nebulizer is titrated on 6 micrograms breath-to-breath equivalence. And Tyvaso DPI uses -- I believe it's 16 micrograms. So there’s subtle differences between how much breath by breath is being delivered, but these are -- Yutrepia has comparable bioavailability relative to Tyvaso nebulizers.).

<sup>121</sup> Compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022, -027 with INCREASE Protocol (UTC\_PH-ILD\_145360) at -470-471; *supra* § III.D.2.a; *infra* § IV.A.2.b.

<sup>122</sup> Compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022, -027 with 2022 Tyvaso Label (UTC\_PH-ILD\_005268) at -269 and 2022 Tyvaso DPI Label (UTC\_PH-ILD\_010709) at -710--711; *infra* § IV.A.2.b.

<sup>123</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022, -027; *infra* § IV.A.2.b.

may be administered at least in view of its conversion table instructing that 132.5µg and 159µg of “YUTREPIA Dose” corresponds to “≥15 and ≤17” and “≥18” Tyvaso breaths.<sup>124</sup>

119. As noted above, the tentatively approved Yutrepia label provides tables converting its capsule dosage into estimated delivered dosage and correlating Tyvaso breaths with Yutrepia capsules.<sup>125</sup> These conversion tables reveal that the dosing instructions provided by Yutrepia’s tentatively approved label’s “2 Dosage AND ADMINISTRATION” section of the “FULL PRESCRIBING INFORMATION” and “DOSAGE AND ADMINISTRATION” section of the “HIGHLIGHTS OF PRESCRIBING INFORMATION” align with the dosing regimen of the INCREASE study.<sup>126</sup> The “26.5 mcg 3 to 5 times per day” initial dose for patients naïve to treprostinil aligns with the initial dosages administered during the INCREASE study.<sup>127</sup> Yutrepia’s tentatively approved label’s instruction to increase doses by 26.5µg per dose each week as tolerated, aligns with the rate at which Tyvaso dosing was titrated upward during the INCREASE study.<sup>128</sup> Moreover, Yutrepia’s target maintenance dosage (79.5µg to 106µg) correspond to the INCREASE study’s target and maximum doses respectively.<sup>129</sup> Accordingly the tentatively approved Yutrepia label twice instructs administering Yutrepia to PH-ILD patients consistent with the INCREASE study.<sup>130</sup>

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<sup>124</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022; *infra* § IV.A.2.b.

<sup>125</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-032, -027; *infra* § IV.A.2.b.

<sup>126</sup> *Compare* Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021-032, -027 with INCREASE Protocol (UTC\_PH-ILD\_145360) at -470-471; *supra* §§ III.D.2, IV.A.1; *infra* § IV.A.2.b.

<sup>127</sup> *Compare* Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021-032, -027 with INCREASE Protocol (UTC\_PH-ILD\_145360) at -470-471; *supra* §§ III.D.2, IV.A.1; *infra* § IV.A.2.b.

<sup>128</sup> *Compare* Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021-032, -027 with INCREASE Protocol (UTC\_PH-ILD\_145360) at -470-471; *supra* §§ III.D.2, IV.A.1; *infra* § IV.A.2.b.

<sup>129</sup> *Compare* Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021-032, -027 with INCREASE Protocol (UTC\_PH-ILD\_145360) at -470-471; *supra* §§ III.D.2, IV.A.1; *infra* § IV.A.2.b.

<sup>130</sup> *Compare* Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021-032, -027 with INCREASE Protocol (UTC\_PH-ILD\_145360) at -470-471; *supra* §§ III.D.2, IV.A.1; *infra* § IV.A.2.b.

**2. Liquidia relies on Tyvaso data for regulatory approval of Yutrepia indicated for pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability**

**a. Liquidia pursued approval for Yutrepia via the 505(b)(2) pathway, including for the PH-ILD indication**

120. Liquidia's internal reference for its Yutrepia product is LIQ861.<sup>131</sup> Liquidia submitted the original IND for LIQ861 on September 30, 2016 (IND 129819).<sup>132</sup> However, in a May 9, 2016 Pre-IND meeting, Liquidia discussed the prospects of pursuing the above-recited PAH indication for its Yutrepia product via that 505(b)(2) pathway and electing to use Tyvaso as the reference list drug.<sup>133</sup> Liquidia admitted that its product had that same active ingredient as Tyvaso and would be administered by the same inhaled route, but Liquidia proposed that its product's "different dosage form (inhalation powder versus liquid aerosol), includes differences in excipients, and requires a different inhalation device (DPI versus nebulizer)" justified the 505(b)(2) pathway.<sup>134</sup> FDA indicated that Liquidia's proposal "appear[ed] acceptable, at th[at] time, based on the available information," but expressly noticed Liquidia of the implications of pursuing 505(b)(2) approval:<sup>135</sup>

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<sup>131</sup> IND 129819 SN0001 Cover Letter (LIQ\_PH-ILD\_00022878) at -878; IND 129819 Application (LIQ\_PH-ILD\_00022883) at -883.

<sup>132</sup> *E.g.*, Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -026.

<sup>133</sup> Pre-IND meeting (LIQ\_PH-ILD\_00046114) at -115-118; *see also* Rajeev Saggat Dep. Tr. at 68:14-69:4 (Q. You say that, at the time you did a Yutrepia and Tyvaso comparative bioavailability study in healthy volunteers -- at that time, Liquidia was already intending to use the results of that study to seek an indication for PH-ILD for Yutrepia? A. Well, at that time, the regulatory pathway was a 505(b)(2) strategy, with the referenced drug using Tyvaso. That -- the regulatory agreement with the agency was to conduct a specific set of studies that would then, if agreed upon that it was safe, and have comparable bioavailability, that it can be reviewed for effectively approval for PAH at that time. At that time that you're alluding to, the approval -- Tyvaso's approval for PH-ILD had not been granted.); *see supra* §§ III.C, IV.A.1.

<sup>134</sup> Pre-IND meeting (LIQ\_PH-ILD\_00046114) at -115-118; *see supra* §§ III.C, IV.A.1.

<sup>135</sup> Pre-IND meeting (LIQ\_PH-ILD\_00046114) at -118; *see supra* §§ III.C, IV.A.1.

***FDA Response to Question 1:*** A 505(b)(2) application appears acceptable, at this time, based on the available information. Please note that if a 505(b)(2) application relies for approval, in part, on FDA’s finding of safety and/or effectiveness for one or more listed products, the applicant must establish that such reliance is scientifically appropriate. The applicant should establish a “bridge” (e.g., via comparative bioavailability data) between the proposed product and each listed drug on which the applicant proposes to rely to demonstrate that such reliance is scientifically justified. For additional information for sponsors considering the submission of an application through the 505(b)(2) pathway, see the 505(b)(2) REGULATORY PATHWAY section later in this document.

Of particular relevance to Liquidia, who indicated their intention to rely on Tyvaso, are the instructions that “applicant[s] should establish a ‘bridge’ . . . between the proposed product and each listed drug on which the applicant proposes to rely to demonstrate that such reliance is scientifically justified.”<sup>136</sup> The further instruction recommends, among other things, that sponsors “consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999).”<sup>137</sup> These instructions further emphasize that sponsors must submit data to support the reliance on the RLD.<sup>138</sup> It also instructs:<sup>139</sup>

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
1. Example: Published literature	Nonclinical toxicology
2. Example: NDA XXXXXX “TRADENAME”	Previous finding of effectiveness for indication X
3. Example: NDA YYYYYY “TRADENAME”	Previous finding of safety for Carcinogenicity, labeling section XXX

<sup>136</sup> Pre-IND meeting (LIQ\_PH-ILD\_00046114) at -115-118; *see supra* §§ III.C, IV.A.1.

<sup>137</sup> Pre-IND meeting (LIQ\_PH-ILD\_00046114) at -132-134; *see supra* § III.C.

<sup>138</sup> Pre-IND meeting (LIQ\_PH-ILD\_00046114) at -132; *see supra* § III.C

<sup>139</sup> Pre-IND meeting (LIQ\_PH-ILD\_00046114) at -132-134; *see supra* § III.C.

This is not the only time Liquidia received this notice, as it was included in both May 11, 2017 and June 6, 2017 correspondence regarding a May 17, 2017 Type B End of Phase 1 meeting.<sup>140</sup> It was also included in correspondence arising from Liquidia's November 19, 2019 Pre-NDA meeting submission.<sup>141</sup>

121. In that November 2019 Pre-NDA meeting request, Liquidia inquired whether FDA “agree[d] that a PK bridge ha[d] been established between [Yutrepia] and the reference listed drug, Tyvaso, to support a 505(b)(2) NDA for [Yutrepia] relying on the FDA’s previous finding of safety and effectiveness for Tyvaso, the RLD[.]”<sup>142</sup> Liquidia was expressly referencing the data it had generated from its LTI-102 study—a comparative bioavailability study that I discuss in greater detail below.<sup>143</sup> FDA agreed, stating that the “presented exposure comparisons are reasonable.”<sup>144</sup> Less than three months later (January 24, 2020), Liquidia submitted an original 505(b)(2) application for LIQ861 (NDA 213005) listing Tyvaso as the reference listed drug (RLD; NDA 022387) and seeking approval for Tyvaso’s PAH indication.<sup>145</sup>

122. Liquidia’s 505(b)(2) application admits that “Tyvaso shares the same active ingredient (treprostinil), route of administration (oral inhalation), and indication (PAH) with [Yutrepia],” but continues to assert the 505(b)(2) pathway is appropriate because Yutrepia’s

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<sup>140</sup> May 11, 2017 Correspondence (LIQ\_PH-ILD\_00046101) at -103, -110-113; June 6, 2017 Correspondence (LIQ\_PH-ILD\_00046141) at -142, -152-155.

<sup>141</sup> Pre-NDA meeting (LIQ\_PH-ILD\_00046156) at -158, -171-172.

<sup>142</sup> Pre-NDA meeting (LIQ\_PH-ILD\_00046156) at -163; *see supra* §§ III.C, IV.A.1; *infra* § IV.A.2.b.

<sup>143</sup> Pre-NDA meeting (LIQ\_PH-ILD\_00046156) at -163; *infra* § IV.A.2.b.

<sup>144</sup> Pre-NDA meeting (LIQ\_PH-ILD\_00046156) at -163; *see supra* §§ III.C, IV.A.1; *infra* § IV.A.2.b.

<sup>145</sup> Original NDA Cover Letter (LIQ\_PH-ILD\_00045978) at -978-979; Original 505(b)(2) Application (LIQ\_PH-ILD\_00046054) at -054-058; *see supra* §§ III.C, IV.A.1.

“dosage form and formulation of LIQ861 differ from that of Tyvaso.”<sup>146</sup> Yet the application describes the formulation merely differing as follows:<sup>147</sup>

The LIQ861 formulation includes three novel excipients that, although previously used in approved products, are being used for the first time by the inhalation route (trehalose and leucine) or at a level greater than previously approved inhalation products (polysorbate 80). Trehalose, leucine, and polysorbate 80 have generally recognized as safe status, and leucine and polysorbate 80 are on FDA’s Food Additive List. In addition to the nonclinical studies conducted by the Applicant (section 2.6.1.6.1), this 505(b)(2) NDA also relies in part on published literature for some nonclinical studies to support the safety of these excipients.

And the application’s nonclinical studies established that these excipients are safe to inhale.<sup>148</sup>

123. In view of these so-called differences, Liquidia’s application states that:

The NDA for LIQ861 inhalation powder is submitted in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, relying on the FDA’s previous finding of safety and effectiveness for Tyvaso, the selected reference listed drug (RLD) for demonstration of the effectiveness of treprostinil in the treatment of PAH. Studies to demonstrate the efficacy of treprostinil were performed by the manufacturer of Tyvaso and are referenced via the 505(b)(2) pathway and FDA’s previous finding of safety and effectiveness for Tyvaso to meet the regulatory requirements for that information. *Accordingly, the Applicant did not repeat efficacy studies with LIQ861 (treprostinil) inhalation powder.*<sup>149</sup>

Liquidia’s 505(b)(2) application also lists the clinical information that it is relying on for approval, stating that “[t]he clinical information used to support this submission is displayed in Table 2.5-1[,]” which is reproduced immediately below:<sup>150</sup>

<sup>146</sup> Original NDA 213005 § 2.6.1 (LIQ\_PH-ILD\_00045498) at -500-503; *see supra* §§ III.C, IV.A.1.

<sup>147</sup> Original NDA 213005 § 2.6.1 (LIQ\_PH-ILD\_00045498) at -503; *see supra* §§ III.C, IV.A.1.

<sup>148</sup> Original NDA 213005 § 2.6.1 (LIQ\_PH-ILD\_00045498) at -503-504; Original NDA 213005 § 3.2.P.4.6 (LIQ\_PH-ILD\_00062236) at -236-244.

<sup>149</sup> Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-516 (emphasis added); *see supra* §§ III.C, IV.A.1.

<sup>150</sup> Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; *see also* Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -360-362; *see supra* §§ III.C, IV.A.1.

Table 2.5-1. Clinical Information Supporting the LIQ861 Submission	
CTD Section	Source of Information
Biopharmaceutics (Module 2.7.1)	Reports of in vitro assessments and bioanalytical reports for studies conducted by or on behalf of the Applicant.
Clinical Pharmacology (Module 2.7.2)	<p>FDA's previous finding of safety and effectiveness for Tyvaso, the RLD for PK and pharmacodynamic characterization of treprostinil, the active ingredient in LIQ861.</p> <p><u>PK Bridge to RLD</u></p> <p>Study LTI-102: A Phase 1 Study to Evaluate the Comparative Bioavailability of Treprostinil Between LIQ861 and Tyvaso® in Healthy Males and Females.</p> <p><u>Supportive PK Studies</u></p> <p>Study LTI-101: A Two-Part Phase 1 Study in Healthy Male and Female Volunteers Consisting of a Randomized, Placebo-Controlled, Double-Blinded, Single-Ascending Dose Study Evaluating the Pharmacokinetics and Safety of LIQ861 via Dry Powder Inhaler and a Two-Sequence, Two-Period, Crossover Study to Evaluate the Performance of Two Dry Powder Inhaler Models.</p> <p>PK Sub-Study of LTI-301: A Pharmacokinetic Sub-Study in a Phase 3 Open-Label, Multicenter Study to Evaluate the Long-Term Safety and Tolerability of Inhaled LIQ861 (Treprostinil) in Pulmonary Arterial Hypertension (WHO Group 1) Patients.</p>
Efficacy (Module 5.3.5.3.1 and 2.7.3)	<p>FDA's previous finding of safety and effectiveness for Tyvaso, the RLD for demonstration of the efficacy of treprostinil, the active ingredient in LIQ861, for the treatment of adults with PAH (WHO Group 1).</p> <p><u>Supportive Study (exploratory efficacy endpoints)</u></p> <p>Study LTI-301: A Phase 3 Open-Label, Multicenter Study to Evaluate the Long-Term Safety and Tolerability of Inhaled LIQ861 (Treprostinil) in Pulmonary Arterial Hypertension (WHO Group 1) Patients.</p>
Safety (Module 5.3.5.3.2 and 2.7.4)	<p>FDA's previous finding of safety and effectiveness for Tyvaso, the RLD with adequate size and duration of clinical safety database to demonstrate tolerability and long-term safety of treprostinil, the active ingredient in LIQ861, for the treatment of adults with PAH (WHO Group 1).</p> <p>Study LTI-301: A Phase 3 Open-Label, Multicenter Study to Evaluate the Long-Term Safety and Tolerability of Inhaled LIQ861 (Treprostinil) in Pulmonary Arterial Hypertension (WHO Group 1) Patients.</p> <p><u>Safety in healthy volunteers</u></p> <p>Study LTI-101: A Two-Part Phase 1 Study in Healthy Male and Female Volunteers Consisting of a Randomized, Placebo-Controlled, Double-Blinded, Single-Ascending Dose Study Evaluating the Pharmacokinetics and Safety of LIQ861 via Dry Powder Inhaler and a Two-Sequence, Two-Period, Crossover Study to Evaluate the Performance of Two Dry Powder Inhaler Models.</p> <p>Study LTI-102: A Phase 1 Study to Evaluate the Comparative Bioavailability of Treprostinil Between LIQ861 and Tyvaso® in Healthy Males and Females.</p> <p>Review of up-to-date literature relevant to safety of treprostinil</p>
CTD = Common Technical Document, FDA = Food and Drug Administration, PAH = pulmonary arterial hypertension, PK = pharmacokinetic, RLD = reference listed drug, WHO = World Health Organization	

124. Table 2.5-1 makes clear that Liquidia is relying on FDA's previous findings of safety and effectiveness for Tyvaso with respect to both clinical safety and effectiveness.<sup>151</sup> This table also expressly identifies LTI-102 as the "PK Bridge to RLD."<sup>152</sup> I also note that Liquidia

<sup>151</sup> Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -518; *see also* Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -360-362; *see also* Rajeev Saggat Dep. Tr. 70:11-72:16; *see supra* §§ III.C.

<sup>152</sup> Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -518; *see also, e.g.,* Original NDA 213005 § 2.7.1 (LIQ\_PH-ILD\_00045396) at -402 (characterizes LTI-102 as the "[d]efinitive PK bridge between Tyvaso and LIQ861 using the intended commercial formulation of LIQ861 in healthy volunteers."); *see supra* §§ III.C, IV.A.2.b.

submitted the results of its Phase 3 study (LTI-301, INSPIRE)—a study that FDA required to demonstrate Yutrepia’s safety and tolerability specifically in PAH patients.<sup>153</sup>

125. On July 24, 2023, Liquidia amended its NDA, adding the PH-ILD indication recited above to Yutrepia’s proposed label.<sup>154</sup> Liquidia reasoned that because Yutrepia “provides for a new dosage form of treprostinil, [and is] relying on Tyvaso . . . as the listed drug” that the amendment was warranted in view of Tyvaso receiving supplemental approval for the above-recited PH-ILD indication in March 2021.<sup>155</sup> Liquidia described the amendment as “afford[ing] alignment with Tyvaso labeling by expanding the [Yutrepia] indication statement to include” the above-recited PH-ILD indication.<sup>156</sup> However, Liquidia amended more than just Yutrepia’s proposed label’s indication statement.<sup>157</sup> This amendment further revised Yutrepia’s proposed label to also refer to the INCREASE study’s patient population and include a summary of the INCREASE study to “CLINICAL STUDIES” section of the “FULL PRESCRIBING INFORMATION,” which expressly recites the INCREASE study’s 6MWD and clinical worsening event due to interstitial lung disease findings.<sup>158</sup> Notably, Liquidia did not otherwise adjust course with respect to pursuing the 505(b)(2) pathway for Yutrepia’s approval.<sup>159</sup>

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<sup>153</sup> Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; *see also* Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -360-362; Pre-IND meeting (LIQ\_PH-ILD\_00046114) at -128-129; *see supra* § III.C.

<sup>154</sup> Yutrepia PH-ILD sNDA (LIQ\_PH-ILD\_00091023) at -023-024; Amendment Cover Letter (LIQ\_PH-ILD\_00091022) at -022; Amended Proposed Label (LIQ\_PH-ILD\_00091129) at -129-130, -139-142; *supra* § IV.A.1; *infra* § IV.A.3.

<sup>155</sup> Amendment Cover Letter (LIQ\_PH-ILD\_00091022) at -022; *supra* § IV.A.1; *supra* § IV.A.1; *infra* § IV.A.3.

<sup>156</sup> Amendment Cover Letter (LIQ\_PH-ILD\_00091022) at -022; *supra* § IV.A.1; *infra* § IV.A.3.

<sup>157</sup> Amended Proposed Label (LIQ\_PH-ILD\_00091129) at -129-130, -139-142; *supra* § IV.A.1; *infra* § IV.A.3.

<sup>158</sup> Amended Proposed Label (LIQ\_PH-ILD\_00091129) at -129-130, -139-142; *supra* § IV.A.1; *infra* § IV.A.3.

<sup>159</sup> Yutrepia PH-ILD sNDA (LIQ\_PH-ILD\_00091023) at -023; Amendment Cover Letter (LIQ\_PH-ILD\_00091022) at -022; *supra* § IV.A.1.

126. On August 16, 2024, FDA tentatively approved Yutrepia for both Tyvaso's PAH and PH-ILD indications.<sup>160</sup> Notably FDA took this action on a 505(b)(2) application in the absence of any clinical data reflecting Yutrepia administration to PH-ILD patients, e.g., the regulatory logs that Liquidia supplied for NDA 213005 indicate that Liquidia has yet to provide to FDA any data reflecting Yutrepia in PH-ILD patients.<sup>161</sup> Liquidia's CMO, Dr. Rajeev Saggar,<sup>162</sup> confirmed this

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<sup>160</sup> Yutrepia label (LIQ\_PH-ILD\_00126017) at -017-018, -055; *supra* § IV.A.1.

<sup>161</sup> LIQ\_PH-ILD\_00130687; LIQ\_PH-ILD\_00130689; *supra* § IV.A.1; *infra* § IV.A.2.c.

<sup>162</sup> D.I. 136; I understand that Rajeev Saggar was designated as a Rule 30(b)(6) corporate representative for Liquidia on corporate topic numbers 1 (Liquidia's research and development activities related to the development of treatment regimens to improve exercise capacity in patients with PH-ILD, including any Liquidia NDA Product.), 2 (Research and development activities performed by or on behalf of Liquidia regarding the administration of Yutrepia to patients having PH-ILD including all relevant pre-clinical or clinical studies or trials.), 3 (Liquidia's communications, collaborations, contracts, and consultations with consultants, experts, clinicians or other third parties regarding the research and development of Yutrepia for PH-ILD.), 6 (Liquidia's knowledge regarding any comparative studies relating the safety and efficacy of TYVASO®, TYVASO DPI®, or any Treprostinil Product to Yutrepia.), 7 (The bases for Liquidia's decision to represent to the FDA that Yutrepia is safe and effective for PH-ILD patients in Liquidia's NDA Amendment.), 8 (How Yutrepia compares to or differs from Tyvaso®, Tyvaso DPI®, or any Treprostinil Product including with respect to patient population, target market, delivery device, dosage, efficacy, safety, and product quality.), 9 (Liquidia's regulatory submissions for Yutrepia including: (1) Liquidia's NDA, Liquidia's NDA Amendment, and any subsequent amendments or supplemental NDAs for Yutrepia; (2) All correspondence with FDA relating to Liquidia's NDA and Liquidia's NDA Amendment, and any subsequent amendments or supplemental NDAs for Yutrepia; (3) Liquidia's current regulatory tracking logs, including Liquidia's IND Sequence Tracker, Liquidia's NDA Sequence Tracker, and Liquidia's NDA Regulatory Chronology log; (4) Any IND submitted by or on behalf of Liquidia to FDA concerning the administration of treprostinil to PH-ILD patients; and (5) Any DMF submitted to FDA in connection with or referenced by Liquidia's NDA.), 11 (Any consideration or decision by Liquidia regarding whether or not to modify the proposed package insert or labeling of any Liquidia NDA Product including any analysis, evaluation, investigation, or discussion concerning those considerations and decisions, such as Liquidia's consideration and decision to (or not to) incorporate portions of the INCREASE or ASCENT study results.), 13 (The factual basis for Roger Jeffs's May 14, 2024 statements regarding the existence of "encouraging initial data from our ASCENT trial of YUTREPIA in PH-ILD," as well as that "the expanded PH-ILD market . . . is only marginally penetrated at this time . . . ."), 14, 16, and 17 (Any communications between Liquidia and key opinion leaders ("KOLs") and/or Scientific Advisory Board members between 2009 and 2024 related to the use of any Treprostinil Product for the treatment of PH-ILD.) Rajeev Saggar Dep. Tr. at 12:10-20, 65:22-67:19; Rajeev Saggar Dep. Ex. 3 at 5-8.

at his deposition, stating “[w]e have not done any additional studies outside of the studies [listed in Liquidia’s original NDA], with the exception of LTI 302, which is an ongoing local safety study.”<sup>163</sup> Additionally, Liquidia’s CMO confirmed that Liquidia’s ASCENT study did not begin until after Liquidia amended Yutrepia’s label to include the PH-ILD indication, and the CMO confirmed that “ASCENT has no regulatory status in regards to the FDA’s consideration for approval or [sic] indication of PH-ILD for Yutrepia.”<sup>164</sup> Accordingly, Liquidia’s tentative approval for a PH-ILD indication relies entirely on UTC’s INCREASE data for safety and efficacy and LTI-102 for the bridge that the 505(b)(2) pathway requires.<sup>165</sup>

**b. Liquidia relies on its comparative pharmacokinetic study as its bridge to Tyvaso safety and efficacy data**

127. Liquidia’s 505(b)(2) application for Yutrepia requires a pharmacokinetic bridge to the RLD: Tyvaso.<sup>166</sup> Liquidia relies on the data generated from its LTI-102 study for that bridge.<sup>167</sup>

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<sup>163</sup> Rajeev Saggat Dep. Tr. at 78:3-6; *see id.* at 43:13-17 (Q. How involved were you in the regulatory submissions relating to Liquidia’s request to add a PH-ILD indication for Yutrepia? A. So as long as there was -- since I joined, I was involved in those discussions.), 67:20-68:13 (Q. Let’s look at [30(b)(6)] Topic No. 1. It’s Liquidia’s research and development activities related to the development of treatment regimens to improve exercise capacity in patients with PH-ILD, including any Liquidia NDA product. Do you see that? A. Yes, I do. Q. What research and development has Liquidia done regarding treatment regimens to improve exercise capacity in patients with PH-ILD with respect to Yutrepia? A. So we have done studies in humans. Phase 1, healthy volunteer study, that is a comparable bioavailability study that shows comparable bioavailability between Yutrepia and Tyvaso. We have conducted an open-label safety study called INSPIRE. And those two studies, along with our preclinical work, was done to submit an NDA for both indications, for PAH and PH-ILD.), 77:3-79:9; *supra* § IV.A.1; *infra* § IV.A.2.c.

<sup>164</sup> Rajeev Saggat Dep. Tr. at 79:22-80:13 (Q. Are you familiar with Liquidia’s ASCENT study? A. Yes, I am. Q. And that study began after Liquidia submitted a request to FDA seeking a PH-ILD indication, correct? A. That is correct. Q. And so, as a result of that, the ASCENT study does not really play any role in supporting Liquidia’s request for a PH-ILD indication, correct? A. That is correct. ASCENT has no regulatory status in regards to the FDA’s consideration for approval or indication of PH-ILD for Yutrepia.); *infra* §§ IV.A.2.c, IV.C.

<sup>165</sup> *See, e.g.*, Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; *infra* §§ IV.A.2.b-c.

<sup>166</sup> *E.g.*, Pre-NDA meeting (LIQ\_PH-ILD\_00046156) at -171; *supra* §§ III.C, IV.A.1, IV.A.2.a.

<sup>167</sup> *E.g.*, Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; *supra* §§ III.C, IV.A.1, IV.A.2.a.

LTI-102 evaluated the bioavailability and safety of Yutrepia relative to Tyvaso using healthy subjects, and the results were published in Roscigno et al. (“Roscigno 2021”).<sup>168</sup> Roscigno 2021 asserts that doses for dry powder formulations—like Yutrepia—are provided in terms of capsule strength, which refers to the amount of active ingredient within a capsule (“total capsule fill”), not the output available when inhaled (“target delivered dose”).<sup>169</sup> Roscigno 2021 also explains that target delivered dose is less than the total capsule fill. According to Roscigno 2021, nebulized solutions are, by contrast, dosed based on the target delivered dose.<sup>170</sup>

128. Although Roscigno 2021 purports these two labeling paradigms “are not interchangeable,” Roscigno 2021 then explains that Yutrepia’s 79.5µg capsule strength achieves a 58.1µg target dose that corresponds to the 54µg delivered dose achieved with 9 breaths of Tyvaso (which was Tyvaso’s maintenance dose when LTI-102 was conducted, i.e., before Tyvaso was indicated for PH-ILD).<sup>171</sup> Moreover, the Roscigno 2021 authors are clear that “the dose for LIQ861 (capsule strength 79.5 µg) . . . was chosen because it has a similar target delivered dose (58.1 µg) as the chosen Tyvaso® dose (labeled dose strength same as target delivered dose) of 54 µg.”<sup>172</sup> It therefore appears to be no coincidence that the tentatively approved Yutrepia label sets the 79.5µg capsule strength as the lower limit of the recited target maintenance dose.<sup>173</sup> Nonetheless, Roscigno 2021 states that the primary objective of LTI-102 was to assess the comparative bioavailability of these respective doses of Yutrepia and Tyvaso.<sup>174</sup>

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<sup>168</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>169</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>170</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>171</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666; 2009 Tyvaso Label (UTC\_PH-ILD\_010692) at -694; *supra* § III.D.1.

<sup>172</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>173</sup> Yutrepia label (LIQ\_PH-ILD\_00126017) at -022.

<sup>174</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

129. Roscigno 2021 reports that LTI-102 was “a single-center, randomized, open-label, replicate . . . , and crossover . . . study in healthy adults.”<sup>175</sup> Subjects were randomized 4:1:1 to the “Replicate Group, Comparative Bioavailability Group 1, and Comparative Bioavailability Group 2,” respectively.<sup>176</sup> Subjects in the Replicate Group received two Yutrepia treatments.<sup>177</sup> Subjects in Comparative Bioavailability Group 1 and Comparative Bioavailability Group 2 received a Yutrepia dose and a Tyvaso dose with the order inversed between the two groups.<sup>178</sup> Doses were provided on consecutive days, with data collected before dosing and throughout the 6 hours following dosing.<sup>179</sup> Subjects remained at the clinical site overnight.<sup>180</sup> Samples were collected before dosing and at 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, and 360 minutes after the dose.<sup>181</sup> Some variability was permitted:  $\pm 1$  minute for the 5, 10, 15, and 20-minute timepoints;  $\pm 5$  minutes for the 30, 45, and 60-minute timepoints; and  $\pm 10$  minutes for the remainder.<sup>182</sup>

130. The study enrolled healthy male and female subjects between 18 and 45 years of age (inclusive), with a body mass index (BMI) of 18 to 32 kg/m<sup>2</sup>, who abstained from tobacco and nicotine use for at least 2 months prior to screening.<sup>183</sup> Subjects were instructed not to take any prescription medication for 14 days or any dietary supplements or over-the-counter drugs for at least 3 days prior to CRU admission through completion of the study.<sup>184</sup> The study excluded those who: “had a history of asthma or other respiratory condition; a history of illicit drug or alcohol

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<sup>175</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>176</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>177</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>178</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>179</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>180</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>181</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>182</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>183</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>184</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

abuse or positive urine drug screen; were positive for human immunodeficiency virus, hepatitis B, and/or hepatitis C; were pregnant or lactating females; had clinically significant medical or psychiatric history that, in the Investigator's judgment, would compromise the subject's safety or the collection of data; had donated plasma or blood within 7 or 30 days prior to [the clinical site] admission, respectively; had participated in another investigational drug study within 30 days prior to [the clinical site] admission; or had surgery within 6 months prior to screening.”<sup>185</sup>

131. In total, 24 subjects enrolled, and 23 subjects completed the study.<sup>186</sup> One subject in the Replicate Group discontinued after receiving their first Yutrepia treatments.<sup>187</sup> The mean data for the Replicate Group and Comparative Bioavailability Groups are reproduced below:<sup>188</sup>

Treatment	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>last</sub> (h*ng/mL)	AUC <sub>inf</sub> (h*ng/mL)	t <sub>1/2</sub> (h)
<b>Replicate Group</b>					
LIQ861 Dose 1 (n = 16)	1.25 (0.505)	0.17 (0.10, 0.57)	0.975 (0.196)	1.01 (0.196)	0.647 (0.142)
LIQ861 Dose 2 (n = 15)	1.28 (0.378)	0.17 (0.08, 0.50)	0.950 (0.216)	0.995 (0.209)	0.610 (0.164)
<b>Comparative Bioavailability Groups</b>					
LIQ861 (n = 8)	1.48 (0.668)	0.13 (0.06, 0.33)	1.01 (0.0926)	1.04 (0.102)	0.546 (0.117)
Tyvaso® (n = 8)	1.60 (0.722)	0.17 (0.13, 0.25)	1.09 (0.217)	1.14 (0.196)	0.520 (0.0925)

AUC<sub>inf</sub> = area under the plasma concentration versus time curve from time 0 extrapolated to infinite time;  
AUC<sub>last</sub> = AUC from time 0 to time of the last measurable non-zero plasma concentration; C<sub>max</sub> = maximum observed plasma concentration; PK = pharmacokinetic; SD = standard deviation; t<sub>1/2</sub> = half-life; T<sub>max</sub> = time to C<sub>max</sub>.  
Data are from the 16 subjects in the Replicate Group who took single doses of LIQ861 on 2 occasions (except for one subject who did not take the second dose) and the 8 subjects in the Comparative Bioavailability Groups who took one dose of LIQ861 and one dose of Tyvaso®. There were 4 subjects in each of the 2 Comparative Bioavailability Groups who took the 2 treatments in the opposite order.  
Data are mean (SD) for all parameters except for T<sub>max</sub> which is median (minimum, maximum).

The plasma treprostnil concentration curves are reproduced below for these groups:<sup>189</sup>

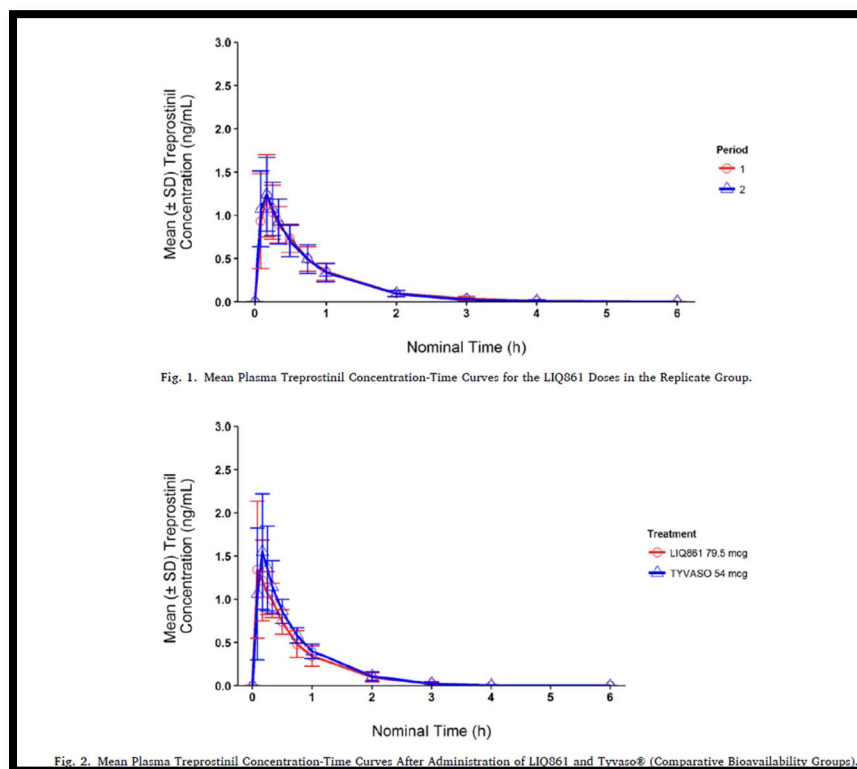
<sup>185</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>186</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -667.

<sup>187</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -667.

<sup>188</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -667.

<sup>189</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -668.



These curves show when inhaled treprostinil is administered; the maximum amount to enter the bloodstream (the height of the peak concentration-time curve); the time it takes to reach the maximum amount (the time at which the maximum is achieved); and the total amount in the blood (the area beneath the concentration-time curve) is essentially the same for Tyvaso and Yutrepia (LIQ861).

132. The pharmacokinetic data from Comparative Bioavailability Groups were processed according to standard statistical approach for calculating bioequivalence—average bioequivalence.<sup>190</sup> The Least Squares Geometric Mean ratios of LIQ861 (79.5 µg): Tyvaso® (54

<sup>190</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -667-668; FDA GFI 2001 Statistical Approaches to Establishing BE (UTC\_PH-ILD\_227453) at -456-460; FDA Draft GFI 2022 Statistical Approaches to Establishing BE (UTC\_PH-ILD\_227501) at -504-506, -514-516.

µg) for each pharmacokinetic parameter ( $C_{max}$ ,  $AUC_{inf}$ , and  $AUC_{last}$ ) expressing the relative bioavailability are reproduced below along with the 90% confidence intervals for those ratios:<sup>191</sup>

Table 2 Comparative Bioavailability Results.		
Treprostnil PK Parameter	LS GMR	
	Point Estimate	90% CI
$AUC_{inf}$	0.923	(0.802, 1.064)
$AUC_{last}$	0.947	(0.812, 1.103)
$C_{max}$	0.931	(0.819, 1.059)

$AUC_{inf}$  = area under the plasma concentration versus time curve from time 0 extrapolated to infinite time;  
 $AUC_{last}$  = AUC from time 0 to time of the last measurable non-zero plasma concentration; CI = confidence interval;  $C_{max}$  = maximum observed plasma concentration; LS GMR = Least Squares Geometric Mean Ratio LIQ861 (79.5 µg): Tyvaso® (54 µg); PK = pharmacokinetic.  
 Data are from the 8 subjects in the Comparative Bioavailability Groups.

The full range of the confidence intervals for each pharmacokinetic parameter is within the range FDA considers bioequivalent (80%-125%), and thus would otherwise be considered bioequivalent.<sup>192</sup> Although Roscigno 2021 does not use the term bioequivalent, it acknowledges that the corresponding 90% confidence intervals were entirely within the 80%-125% range, and thus implicitly acknowledges bioequivalence.<sup>193</sup> Otherwise, Roscigno 2021 concludes that Yutrepia and Tyvaso “exposure” and “bioavailability” were “comparable.”<sup>194</sup>

<sup>191</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -668.

<sup>192</sup> FDA GFI 2001 Statistical Approaches to Establishing BE (UTC\_PH-ILD\_227453) at -456-460; FDA Draft GFI 2022 Statistical Approaches to Establishing BE (UTC\_PH-ILD\_227501) at -504-506, -514-516.

<sup>193</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -669 (“For  $AUC_{inf}$ ,  $AUC_{last}$ , and  $C_{max}$ , the LS GMRs (LIQ861: Tyvaso®) were between 0.9 and 1.0 with corresponding 90% CIs contained entirely within 0.8 to 1.25.”).

<sup>194</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -669 (“The comparative bioavailability assessment demonstrated that treprostnil exposure from a single capsule dose of 79.5 µg LIQ861 (approximate delivered dose 58.1 µg) is comparable to treprostnil exposure from 9 breaths of Tyvaso® (approximate delivered dose 54 µg); *id.* (“In conclusion, comparable treprostnil bioavailability was demonstrated after administration of LIQ861 (79.5 µg capsule) and Tyvaso® (9 breaths for a 54-mcg dose), and both were well tolerated.”).

133. As noted above the administered doses of each product were selected to achieve comparable delivered doses of treprostinil and to compare Yutrepia to the then target dose for Tyvaso.<sup>195</sup> Roscigno 2021 explains that the respective doses of Yutrepia (79.5µg capsule strength; 58.1µg target delivered dose) and Tyvaso (9 breaths, i.e., a 54µg) were “expected to result in approximately the same treprostinil exposure.”<sup>196</sup> Roscigno 2021 states that this is because target delivered dose “is a more valid comparison of the doses than the labeled dose strength because of the different labeling conventions for the 2 types of drug delivery systems.”<sup>197</sup> Roscigno 2021 also credits earlier results generated from Liquidia’s LTI-101 study—“a randomized, double-blind, placebo-controlled, single ascending dose study.”<sup>198</sup> The authors of Roscigno 2021 also credit LTI-101 for “establish[ing] the dose proportionality of treprostinil exposure and its tolerability after administration of [Yutrepia] (25 to 150 µg dose range).”<sup>199</sup> Moreover, Roscigno 2021 states that the pharmacokinetic data from LTI-101 “was similar to the published treprostinil PK profile after Tyvaso® administration.” Accordingly, in view of LTI-101 and LTI-102, converting between Yutrepia and Tyvaso dosing was routine and formulaic once LTI-102 was completed.

134. Indeed, the Roscigno 2021 authors state that LTI-102 was only conducted to examine the pharmacokinetics of Yutrepia and Tyvaso in the same study.<sup>200</sup> The authors further acknowledge that LTI-102 “was conducted to establish a PK bridge between treprostinil administered as LIQ861 (capsule strength of 79.5 µg and delivered via DPI with target delivered

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<sup>195</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -667, -668-669; 2009 Tyvaso Label (UTC\_PH-ILD\_010692) at -694.

<sup>196</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -668.

<sup>197</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -668.

<sup>198</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -668.

<sup>199</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -668.

<sup>200</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -668-669.

dose of 58.1 µg) and the reference drug, treprostinil solution for inhalation (Tyvaso®) (labeled strength with 9 breaths for a target delivered dose via nebulizer of 54 µg).”<sup>201</sup>

135. As noted above, this pharmacokinetic bridge from Yutrepia to Tyvaso is critical to the success of Liquidia’s 505(b)(2) application, even for the PH-ILD indication.<sup>202</sup> Liquidia was on notice of this from at least as early as its pre-IND meeting.<sup>203</sup> Liquidia, in their pre-NDA meeting correspondence, specifically asked FDA if LTI-102 was sufficient for this purpose, and FDA agreed that it was:<sup>204</sup>

### 2.3. Regulatory

**Question 7: PK bridge for 505(b)(2) pathway:** Data from a comparative bioavailability PK study in healthy subjects (Protocol LTI-102) demonstrate that a 79.5 mcg dose of treprostinil from LIQ861 delivered by dry powder inhaler and a 54 mcg dose of treprostinil from Tyvaso delivered by nebulizer result in similar treprostinil systemic exposure. Does the Agency agree that a PK bridge has been established between LIQ861 and the reference listed drug, Tyvaso, to support a 505(b)(2) NDA for LIQ861 relying on the FDA’s previous finding of safety and effectiveness for Tyvaso, the RLD?

**FDA Response to Question 7:** Yes, the presented exposure comparisons are reasonable.

**Additional Comment:**

We note that the lowest strength of your product is 26.5 mcg. However, as per Tyvaso’s prescribing information, the starting dose is 3 breaths (18 mcg) per session, which, if not tolerated, is reduced to 1 (6 mcg) or 2 (12 mcg) breaths per session. While your lowest strength (26.5 mcg) can support initiation at 3 breaths per session, it does not allow a patient to use your product for initiation if 3 breaths per session is not tolerated. Please address your plans to develop a strength lower than 26.5 mcg.

Moreover, Liquidia’s original NDA repeatedly characterizes LTI-102 as “provid[ing] the definitive PK bridge to [Tyvaso],” “PK bridge to the RLD,” etc.<sup>205</sup> In fact, Liquidia’s 505(b)(2)

<sup>201</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -668; *supra* §§ III.C, IV.A.2.a.

<sup>202</sup> *Supra* §§ III.C, IV.A.1, IV.A.2.a.

<sup>203</sup> Pre-IND meeting (LIQ\_PH-ILD\_00046114) at -115-118, -132-133; *supra* §§ III.C, IV.A.2.a.

<sup>204</sup> Pre-NDA meeting (LIQ\_PH-ILD\_00046156) at -163; *supra* §§ III.C, IV.A.2.a.

<sup>205</sup> *E.g.*, Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -362; Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -518; *see also, e.g.*, Original NDA 213005 § 2.7.1 (LIQ\_PH-ILD\_00045396) at -402 (characterizes LTI-102 as the “[d]efinitive PK bridge between Tyvaso and

application expressly, recounts the pre-NDA meeting and that “FDA agreed that an adequate PK bridge to Tyvaso was established.”<sup>206</sup> Also, as discussed above, Table 2.5-1 characterizes LTI-102 as establishing the requisite 505(b)(2) bridge to Tyvaso.<sup>207</sup> As noted above, when Liquidia amended its label, Liquidia did not otherwise adjust course with respect to pursuing the 505(b)(2) pathway for Yutrepia’s approval.<sup>208</sup>

136. I also note that the tentatively approved Yutrepia label recites the absorption pharmacokinetic data from LTI-102:<sup>209</sup>

### **12.3 Pharmacokinetics**

#### Absorption

in healthy volunteer studies, the systemic exposure (AUC and  $C_{max}$ ) post-inhalation was shown to be proportional to the YUTREPIA doses administered (25 mcg – 150 mcg). The treprostinil mean  $C_{max}$ , mean  $AUC_{inf}$  and median  $T_{max}$  following a single inhaled target maintenance dose of 79.5 mcg YUTREPIA were 1.48 ng/mL, 1.04 hr.ng/mL and 0.13 hr, respectively.

This also seems to be the case for the provide half-life:<sup>210</sup>

#### Elimination

Following inhaled administration of YUTREPIA, disposition and elimination is monophasic with a half-life of approximately 30 minutes.

137. Roscigno 2021 is a well-done study of its type. The selection of subjects was standard for studies of this type analysis, as were the methods for collection and analysis of

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LIQ861 using the intended commercial formulation of LIQ861 in healthy volunteers.”); *supra* §§ III.C, IV.A.2.a.

<sup>206</sup> *E.g.*, Original NDA 213005 § 2.7.1 (LIQ\_PH-ILD\_00045396) at -402; *supra* §§ III.C, IV.A.2.a.

<sup>207</sup> Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at LIQ\_PH-ILD\_00045518; *supra* §§ III.C, IV.A.2.a.

<sup>208</sup> Yutrepia PH-ILD sNDA (LIQ\_PH-ILD\_00091023) at -023; Amendment Cover Letter (LIQ\_PH-ILD\_00091022) at -022; *supra* § IV.A.2.a; *infra* § IV.A.2.c.

<sup>209</sup> *Compare* Roscigno 2021 (UTC\_PH-ILD\_010665) at -667 with Yutrepia label (LIQ\_PH-ILD\_00126017) at -027.

<sup>210</sup> *Compare* Roscigno 2021 (UTC\_PH-ILD\_010665) at -667 with Yutrepia label (LIQ\_PH-ILD\_00126017) at -028.

pharmacokinetic data and monitoring for potential adverse events.<sup>211</sup> The statistical method for analyzing the pharmacokinetic data and for assessing relative bioavailability—an MMRM model applied to log-transformed individual pharmacokinetic parameters—was also standard.<sup>212</sup>

138. Also, it is typical for bioavailability studies—like Roscigno 2021—to be single center, single arm studies.<sup>213</sup> Although uncontrolled single-center, single-arm studies suffer from the significant drawbacks that I detail above and in my Rebuttal Report,<sup>214</sup> there are three reasons why those drawbacks do not apply to bioavailability studies. First, the issues related to patient referral do not apply because bioavailability studies are conducted in healthy subjects,<sup>215</sup> so the referral basis and treatment expertise of the study center is irrelevant to the bioavailability assessments these studies conduct. Second, bioavailability studies, including Roscigno 2021, examine the same subjects under two treatment conditions, with the results compared within each subject—e.g., a crossover study.<sup>216</sup> This means that any subject-specific characteristic is present for assessment of each treatment, and such effects cancel out when the treatments are compared. These studies are controlled, in that each subject serves as his or her own control. Third, the order in which subjects receive the two treatments is randomized,<sup>217</sup> so any effects that may result from multiple exposures are balanced between the two treatments in such a way that any such effects, if present, can be assessed and accounted for in the statistical analysis.

139. That the LTI-102 study reported a bridge between Tyvaso and Yutrepia is further supported by explicit disclosures in the tentatively approved Yutrepia label. For example, the

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<sup>211</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -666-667.

<sup>212</sup> Roscigno 2021 (UTC\_PH-ILD\_010665) at -667.

<sup>213</sup> *E.g.*, Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>214</sup> Thisted Reb. Rpt. §§ VII, IX, XI, XV; *supra* §§ III.B, III.D.2.c c.

<sup>215</sup> *E.g.*, Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>216</sup> *E.g.*, Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

<sup>217</sup> *E.g.*, Roscigno 2021 (UTC\_PH-ILD\_010665) at -666.

tentatively approved Yutrepia label provides both the Yutrepia capsule strength – delivered dose conversion table and the Tyvaso breath – Yutrepia capsule strength interconversion table detailed above.<sup>218</sup> The tentatively approved Yutrepia label also specifically provides the following regarding the INCREASE study:

Patients in the INCREASE study were randomized (1:1) to either placebo or treprostinil inhalation solution in four daily treatment sessions with a target dose of 9 breaths (equivalent to 79 .5 mcg YUTREPIA) per session and a maximum dose of 12 breaths (equivalent to 106 mcg YUTREPIA) per session over the course of the 16-week study.<sup>219</sup>

This reinforces my opinions regarding the applicability of the beneficial outcomes of the INCREASE study to PH-ILD patients administered Yutrepia according to Yutrepia’s tentatively approved label.

**c. Liquidia relies on UTC’s INCREASE Study to evidence efficacy**

140. As noted above and below, Liquidia amended its NDA on July 24, 2023 to include the above-recited PH-ILD indication.<sup>220</sup> On August 16, 2024 FDA tentatively approved Yutrepia for that PH-ILD indication.<sup>221</sup> According to Liquidia’s regulatory logs for NDA 213005 and CMO Dr. Rajeev Sagar’s testimony, Liquidia has yet to provide FDA any data reflecting Yutrepia in PH-ILD patients.<sup>222</sup> Liquidia’s CMO also confirmed that Liquidia’s ongoing ASCENT study,

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<sup>218</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-032, -027; *supra* § IV.A.1; *infra* § IV.A.1.

<sup>219</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031; *infra* § IV.A.3.

<sup>220</sup> *Supra* §§ IV.A.1, IV.A.2.a; *infra* § IV.A.2.a; Yutrepia PH-ILD sNDA (LIQ\_PH-ILD\_00091023) at -023-024; Amendment Cover Letter (LIQ\_PH-ILD\_00091022) at -022; Amended Proposed Label (LIQ\_PH-ILD\_00091129) at -129-130, -139-142.

<sup>221</sup> *Supra* §§ IV.A.1, IV.A.2.a; *infra* § IV.A.3; Yutrepia label (LIQ\_PH-ILD\_00126017) at -022.

<sup>222</sup> *Supra* § IV.A.2.a; LIQ\_PH-ILD\_00130687; LIQ\_PH-ILD\_00130689; Rajeev Sagar Dep. Tr. at 43:13-17, 67:20-68:13, 77:3-79:9.

which is enrolling PH-ILD subjects, has no regulatory purpose.<sup>223</sup> Accordingly, Liquidia's tentative approval for its PH-ILD indication relies entirely on UTC's INCREASE data for safety and efficacy in PH-ILD patients, and LTI-102 for the bridge between Yutrepia and Tyvaso that the 505(b)(2) pathway requires.<sup>224</sup> Liquidia's tentatively approved Yutrepia label reflects this, reciting nearly identical PH-ILD indication language to that recited in Tyvaso's labels and only citing the INCREASE study and INCREASE data in the section that specifically addresses the clinical support for that PH-ILD indication.<sup>225</sup> Liquidia's CMO testified that "the Liquidia label for Yutrepia copies the same language described in the PH-ILD indication from the Tyvaso label," including improvements in exercise capacity, and relies on the reference label for Tyvaso and "the key results of the INCREASE study."<sup>226</sup>

141. It appears that Liquidia's interest in pursuing a PH-ILD indication is highly intertwined with the INCREASE study, with Liquidia taking note of INCREASE shortly after the top-line results were released in 2020.<sup>227</sup> For example, during the November 2, 2020 LIQ861

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<sup>223</sup> *Supra* § IV.A.2.a; *infra* § IV.C; Rajeev Saggar Dep. Tr. at 79:22-80:13 (Q. Are you familiar with Liquidia's ASCENT study? A. Yes, I am. Q. And that study began after Liquidia submitted a request to FDA seeking a PH-ILD indication, correct? A. That is correct. Q. And so, as a result of that, the ASCENT study does not really play any role in supporting Liquidia's request for a PH-ILD indication, correct? A. That is correct. ASCENT has no regulatory status in regards to the FDA's consideration for approval or indication of PH-ILD for Yutrepia.).

<sup>224</sup> *Supra* §§ III.C, IV.A.2.a-b; Rajeev Saggar Dep. Tr. at 77:3-79:9.

<sup>225</sup> *Supra* § IV.A.1, *infra* § IV.A.3; compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021 with 2022 Tyvaso Label (UTC\_PH-ILD\_005268) at -268-269 and 2022 Tyvaso DPI Label (UTC\_PH-ILD\_010709) at -709-710; see also Rajeev Saggar Dep. Tr. at 84:3-19, 84:24 - 85:1, 85:12-22, 196:10-17.

<sup>226</sup> *Supra* § III.D.2; *infra* § IV.A.3; Rajeev Saggar Dep. Tr. at 84:3-19.

<sup>227</sup> Nov. 2020 LIQ861 Steering Committee Meeting (LIQ\_PH-ILD\_00113881) at -885-886, -893-894; see also Feb. 24, 2020 press release announcing INCREASE results (UTC\_LIQ00063612).

Steering Committee Meeting,<sup>228</sup> Liquidia's then CMO, Dr. Tushar Shah,<sup>229</sup> explained to the committee members that with respect to "LIQ861 R&D Priorities" that "generating data on LIQ861 use in Group 3 PAH" was one of the "six ideas" that Liquidia was "prioritizing" out of "more than 20 ideas for LIQ861 optimization."<sup>230</sup> When committee members were solicited for their feedback on these six ideas and Liquidia's corresponding rationales, one of the outside advisors in attendance—Dr. Robert Franz, MD, from the Mayo Clinic<sup>231</sup>—stated that "[t]he Group 3 concept obviously is a very straightforward one in terms of the appeal of that given the recent results with TYVASO, and is clearly an unmet need in a relatively high-risk population."<sup>232</sup>

142. That 2020 LIQ861 Steering Committee meeting also featured a discussion led by Dr. Gerald O'Brien, MD, Liquidia's Vice President for Clinical Development, Respiratory,<sup>233</sup> regarding a potential open-label study of Yutrepia in PH-ILD that was "being prepared in anticipation of TYVASO soon receiving an indication for use in this patient population".<sup>234</sup>

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<sup>228</sup> Rajeev Saggar Dep. Tr. at 168:19 -176:23 (Liquidia's CMO describes the purpose of Liquidia's steering committees and advisory Boards, explaining how outside consultants are selected and how the meetings' contents are memorialized.).

<sup>229</sup> Nov. 2020 LIQ861 Steering Committee Meeting (LIQ\_PH-ILD\_00113881) at -884.

<sup>230</sup> *Id.* at -885-886.

<sup>231</sup> *Id.* at -884.

<sup>232</sup> *Id.* at -886; Rajeev Saggar Dep. Tr. at 186:11 - 187:17 (Q. He says that the results of the INCREASE study are, I'll quote, "Clearly an unmet need in a relatively high-risk patient population," correct? A. That is correct. Q. This is an accurate statement of what happened at the Liquidia steering committee meeting on November 2, 2020? A. Yes. He is pointing to results that have been disclosed on the INCREASE study, and he states it is clearly an unmet need. Q. So the carefully selected and respected Dr. Frantz believes that the INCREASE study results address a clearly unmet need in a relatively high-risk patient population, right? A. That is correct.).

<sup>233</sup> Nov. 2020 LIQ861 Steering Committee Meeting (LIQ\_PH-ILD\_00113881). at -884.

<sup>234</sup> *Id.* at -893.

**Group 3**

Dr. O'Brien next reviewed plans for a study assessing the safety and tolerability of transitioning patients who have WHO Group 3 pulmonary hypertension due to iILD from TYVASO to LIQ861. He noted that the study is being prepared in anticipation of TYVASO soon receiving an indication for use in this patient population.

The proposed open-label observational trial would enroll 40 patients, and run for eight weeks or some other period. The primary outcome measures would focus on safety and tolerability, while secondary endpoints would look at change from baseline in 6MWT and NT proBNP levels, evidence of clinical worsening, and change in Treatment Medication Satisfaction Score from baseline to 12 weeks.

Here Dr. Frantz inquired whether such a study would be necessary for regulatory approval.<sup>235</sup> Dr. Shah answered that this was a discussion Liquidia intended to have with FDA, but that “Liquidia [would] not initiate discussions with [FDA] until after Tyvaso receive[d] its approval for use in Group 3 patients.”<sup>236</sup> As detailed above, Dr. Shah’s statements are consistent with the route Liquidia pursued: electing to rely on UTC’s INCREASE data to get its own PH-ILD indication approval.<sup>237</sup> Moreover, Liquidia ultimately did not actually begin studying Yutrepia in PH-ILD until December 2024 when it initiated the ASCENT study.<sup>238</sup>

143. As noted above, Tyvaso was approved for PH-ILD in April of 2021, and (as foreshadowed by Dr. Shah’s November 2020 statements) Liquidia began soliciting advice from FDA regarding amending its Yutrepia NDA to “align” with Tyvaso’s PH-ILD indication.<sup>239</sup> Liquidia’s CMO explained that Liquidia—in view of Tyvaso’s approval for PH-ILD—wanted “to confirm that no additional studies would be required” to add a PH-ILD indication to Yutrepia’s

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<sup>235</sup> *Id.* (“Dr. Frantz asked if it would even be necessary to do the study if the Company secured FDA approval for use of LIQ861 in Group 1 patients.”)

<sup>236</sup> *Id.*

<sup>237</sup> *Supra* §§ IV.A.1, IV.A.2.a-b; Rajeev Saggat Dep. Tr. at 77:3-79:9.

<sup>238</sup> *Supra* § IV.A.2.a; *infra* § IV.C; Rajeev Saggat Dep. Tr. at 79:22-80:13 (Q. Are you familiar with Liquidia’s ASCENT study? A. Yes, I am. Q. And that study began after Liquidia submitted a request to FDA seeking a PH-ILD indication, correct? A. That is correct. Q. And so, as a result of that, the ASCENT study does not really play any role in supporting Liquidia’s request for a PH-ILD indication, correct? A. That is correct. ASCENT has no regulatory status in regards to the FDA’s consideration for approval or indication of PH-ILD for Yutrepia.).

<sup>239</sup> *Supra* § III.D.1; Nov. 2020 LIQ861 Steering Committee Meeting (LIQ\_PH-ILD\_00113881) at -893; Rajeev Saggat Dep. Tr. at 15:9-17:13.

label.<sup>240</sup> According to Liquidia’s CMO, Liquidia was seeking assurances from FDA that Liquidia could rely on UTC’s INCREASE data to get approval for its Yutrepia product indicated for PH-ILD without needing to conduct Liquidia-sponsored clinical trials that administered Yutrepia to PH-ILD patients.<sup>241</sup> Liquidia’s CMO’s testimony was clear that Liquidia acknowledges that Yutrepia’s approval for PH-ILD relies on the INCREASE study and “that Yutrepia should also be granted the same label” as Tyvaso.<sup>242</sup>

144. I note that Liquidia submitted a Type B Pre-sNDA Meeting – Meeting Request Letter under IND 129819 (SN0091) to FDA on April 8, 2022 that proposed expanding Yutrepia’s listed indications to include “treatment of patients with pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.”<sup>243</sup> Liquidia stated that the requested meeting was “to confirm agreement that the completed development is sufficient

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<sup>240</sup> Rajeev Saggarr Dep. Tr. at 17:5-13 (Liquidia’s CMO indicated that Liquidia was probing whether “the datasets that [Liquidia] already submitted, which was inclusive of the comparable bioavailability study, a safety study in PH patients, and with the additional approval of Tyvaso and PH-ILD . . . was sufficient enough to allow for our application to add the addition of PH-ILD to the label.”); Rajeev Saggarr Dep. Tr. at 15:9-21 (Liquidia’s CMO testified that Liquidia requested that “[FDA] provide advice on aligning [Yutrepia’s] label . . . with the new approval for Tyvaso PH-ILD,” Liquidia’s CMO when he used “aligning” he was referring to adding a PH-ILD indication to Yutrepia.).

<sup>241</sup> *Id.* at 15:9-17:13.

<sup>242</sup> *Id.* at 78:7-79:9 (Q. Okay. And so essentially, what you are saying to the FDA is, “We did a comparative bioavailability study to establish a pharmacokinetic bridge to Tyvaso. Tyvaso is effective for PH-ILD; therefore, you should approve our product for PH-ILD as well”; is that correct? A. Yes. That we want -- that, given the fact that we had tentative approval for PAH, and we had asked for general advice, which the FDA provided to us in April. And in construct with that advice, we believed that it was appropriate to not do any additional clinical studies and request an amendment to add PH-ILD, consistent with the 505(b)(2) regulatory pathway. Q. In view of your reliance on the 505(b)(2) pathway and the advice FDA provided you in April, Liquidia believes Yutrepia should be approved for PH-ILD because of the results of the INCREASE study, correct? A. Yes. Because of the label that was granted to Tyvaso for the indication of PH-ILD, we believe that Yutrepia should also be granted the same label.).

<sup>243</sup> Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -026, -028-030; *supra* §§ IV.A.1, IV.A.2.

in scope to support a supplemental New Drug Application (sNDA) to add the PH-ILD, WHO Group 3 indication to the Yutrepia label and reach alignment with the FDA on the content of the label based on the labeling of the reference listed drug, Tyvaso.”<sup>244</sup> Liquidia’s CMO confirmed that the proposed sNDA consisted of “the INCREASE study and supportive data, including the three-years safety data.”<sup>245</sup> Accordingly, the phrase “completed development” as used by Liquidia, in my view, refers to the nonclinical and clinical studies that Liquidia had conducted as of April 8, 2022, which I note did not include any studies characterized as administering Yutrepia to PH-ILD patients.<sup>246</sup>

145. Liquidia’s April 8, 2022 meeting request posed the following three questions to FDA.<sup>247</sup>

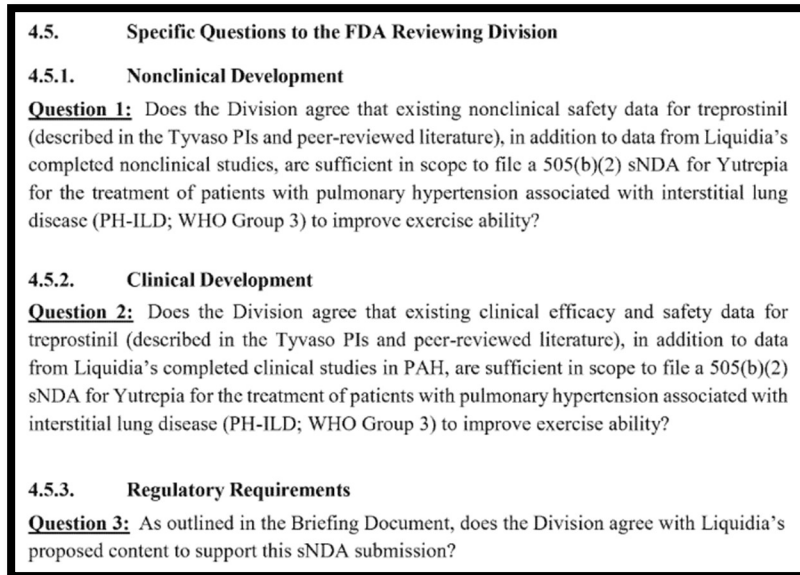
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<sup>244</sup> *Id.* at -029; *see also* Meeting Request Cover Letter (LIQ\_PH-ILD\_00134042) states that “[t]he objective [of the requested meeting] is to confirm agreement that the completed development is sufficient in scope to support a supplemental New Drug Application (sNDA) to add the PH-ILD, WHO Group 3 indication to the Yutrepia label and reach alignment with the FDA on the content of the label based on the labeling of the reference listed drug, Tyvaso.”

<sup>245</sup> Rajeev Saggarr Dep. Tr. at 96:17-97:1.

<sup>246</sup> *See supra* § IV.A.2.a.

<sup>247</sup> Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -030.



Based on these questions, it is clear that Liquidia sought to use the 505(b)(2) pathway for the PH-ILD indication and to not need any further nonclinical or clinical development to obtain approval.<sup>248</sup> The nonclinical and clinical development questions (“Question 1” and “Question 2”) ask whether “existing ... efficacy and safety data for treprostinil (described in Tyvaso PIs and peer-reviewed literature)” is sufficient to obtain approval for the proposed PH-ILD indication, and specifically reference “fil[ing] a 505(b)(2) sNDA” for this indication.<sup>249</sup> I read the phrases “Tyvaso PIs” and “peer-reviewed literature” as used in these questions as referring to the INCREASE study, the INCREASE publication, and other literature describing post-hoc findings from the data generated by the INCREASE study. These questions that Liquidia posed to FDA regarding relying on these data confirm Liquidia intended to rely on the FDA’s findings from UTC supplied data, in particular data and analyses arising from the INCREASE study, to obtain a Yutrepia product indicated for PH-ILD.<sup>250</sup>

<sup>248</sup> Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -030; *supra* §§ III.C, IV.A.1, IV.A.2.a-b.

<sup>249</sup> Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -030; *supra* §§ III.C, IV.A.1, IV.A.2.a-b.

<sup>250</sup> *Supra* §§ III.C, IV.A.1, IV.A.2.a-b; *infra* § IV.A.3.

146. On May 25, 2022, FDA responded to Liquidia's letter, providing written responses to Liquidia's questions and declining a meeting.<sup>251</sup> FDA confirmed that no further data were needed if Liquidia relied on "FDA's previous nonclinical safety findings of Tyvaso [that Liquidia] relied on in the original NDA 213005 via the 505(b)(2) pathway" and "data from the 16-week randomized, double-blind placebo-controlled, multi-center trial (INCREASE) in patients with PH-ILD."<sup>252</sup> Likewise, FDA did not "object to [Liquidia's] plans to include a revised draft of the prescribing information incorporating the PH-ILD indication."<sup>253</sup> Also, FDA expressly acknowledged that Liquidia was proposing to pursue this PH-ILD indication via the 505(b)(2) pathway and provided Liquidia notice of what that entails.<sup>254</sup>

147. Liquidia's CMO testified that Liquidia in view of FDA's answers understood FDA found Liquidia's proposal acceptable.<sup>255</sup> I understand that Liquidia elected to follow this path to approval for the PH-ILD indication.<sup>256</sup> As noted Liquidia's CMO confirmed this, testifying that no other studies have been conducted to support Yutrepia's approval for the PH-ILD indication other than those nonclinical and clinical studies listed in the original NDA and an ongoing open label safety study in PAH patients, and that Liquidia's ASCENT study has no regulatory purpose.<sup>257</sup> Liquidia's CMO's testimony is consistent with a contemporaneous email from Dr. Jennifer Weidman, Liquidia's Vice President of Global Regulatory Affairs.<sup>258</sup> On the same day

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<sup>251</sup> FDA Response (LIQ\_PH-ILD\_00120424) at -424, -426-427, -432.

<sup>252</sup> FDA Response (LIQ\_PH-ILD\_00120424) at -426-427.

<sup>253</sup> FDA Response (LIQ\_PH-ILD\_00120424) at -427.

<sup>254</sup> FDA Response (LIQ\_PH-ILD\_00120424) at -426, -429-431; *Supra* §§ III.C, IV.A.1, IV.A.2.a-b; *infra* § IV.A.3.

<sup>255</sup> Rajeev Saggar Dep. Tr. at 96:14-16; 99:19-21 (Q. And FDA did tell Liquidia it did not need to do efficacy studies in PH-ILD patients, right? A. Yes, they had.).

<sup>256</sup> Rajeev Saggar Dep. Tr. at 78:7-22.

<sup>257</sup> Rajeev Saggar Dep. Tr. at 67:20-68:13, 77:3-79:9, 79:22-80:13; *supra* § IV.A.2.a; *infra* § IV.C.

<sup>258</sup> Weidman Email re: Pre-sNDA Meeting (LIQ\_PH-ILD\_00148509) at -509.

FDA responded to Liquidia's meeting request, Dr. Weidman emailed several Liquidia employees (Tushar Shah, Jason Prabel, Ashley Galloway, Savan Patel, and Marisa Law) with the subject line "attached: IND 129819 Type B Pre-sNDA Meeting Minutes (WRO).pdf", attaching FDA's response letter.<sup>259</sup> In that cover email, Dr. Weidman states that Liquidia had "received our responses to the pre-sNDA meeting questions early," and explains that there was "[n]othing unexpected in these [responses] and we should feel confident that upon eligibility (expiry of exclusivity for the Group 3 indication), we will be able to expand our indication statement to include this new patient population without additional preclinical or clinical data."<sup>260</sup>

148. On May 20, 2023, Liquidia's PH-ILD Advisory Board met and, according to the executive summary, an invited outside expert—Dr. Franck Rahagi from the Cleveland Clinic<sup>261</sup>—gave a presentation regarding the design, patient demographics, and results of the INCREASE study.<sup>262</sup> The executive summary notes that Dr. Rahagi explained "that because Liquidia was 'going to inherit the indication [for PH-ILD granted to inhaled Tyvaso on the basis of INCREASE], they're going to inherit the INCREASE study' and its outcomes."<sup>263</sup> Liquidia's CMO Dr. Rajeev Sagggar was asked about this statement.<sup>264</sup> Dr. Sagggar acknowledged "[Liquidia] relied on the reference label drug Tyvaso, and [Liquidia] submitted a totality of package in which the key results of the INCREASE study were part of that."<sup>265</sup> Dr. Sagggar acknowledged that Liquidia had nothing to do with the INCREASE study, but he stated that Liquidia "deserved" to rely on INCREASE

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<sup>259</sup> Weidman Email re: Pre-sNDA Meeting (LIQ\_PH-ILD\_00148509) at -509, -510-518 (attaching LIQ\_PH-ILD\_00148510 at -510-518).

<sup>260</sup> *Id.* at -509.

<sup>261</sup> May 20, 2023 PH-ILD Advisory Board (LIQ\_PH-ILD\_00122627) at -651.

<sup>262</sup> May 20, 2023 PH-ILD Advisory Board (LIQ\_PH-ILD\_00122627) at -627, -633-636.

<sup>263</sup> May 20, 2023 PH-ILD Advisory (LIQ\_PH-ILD\_00122627) at -633.

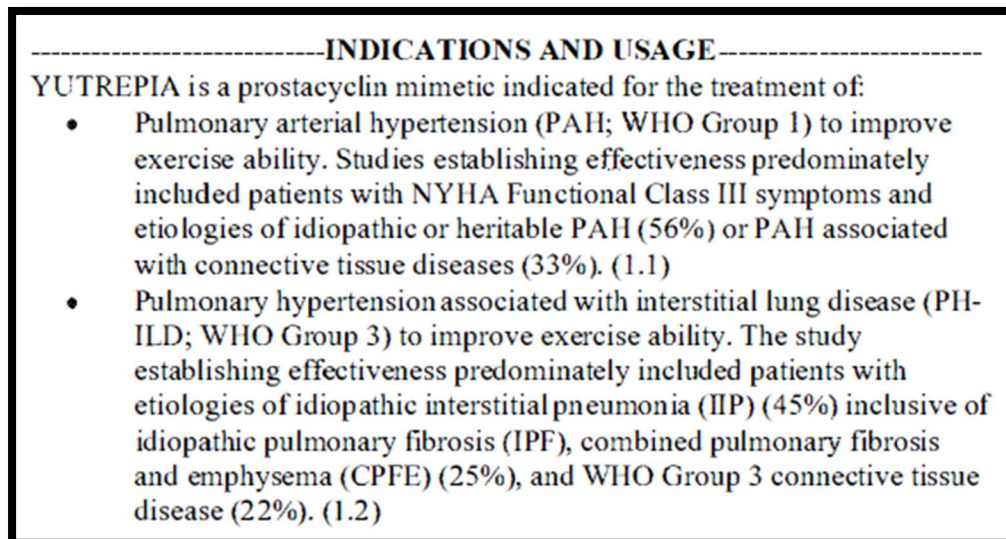
<sup>264</sup> Rajeev Sagggar Dep. Tr. at 195:20-197:23.

<sup>265</sup> Rajeev Sagggar Dep. Tr. at 196:13-17; *supra* §§ III.C, IV.A.1, IV.A.2.a-b.

and its findings as “part of the 505(b)(2) process” and associated regulatory statutes.<sup>266</sup> Dr. Saggar further testified that Liquidia’s 505(b)(2) application for a PH-ILD indication “is reliant on . . . the dataset that the FDA has used for approving Tyvaso for PH-ILD,” conceding that it is the INCREASE study that provides the only PH-ILD patient data upon which Liquidia rests its representations to FDA that Yutrepia is safe and effective in PH-ILD patients.<sup>267</sup>

### 3. The Yutrepia label explicitly references the INCREASE study

149. As noted above, Liquidia proposed amendments to Yutrepia’s label when it amended its NDA on July 24, 2023<sup>268</sup>. These amendments included adding the PH-ILD indication under the “INDICATIONS AND USAGE” section of the “HIGHLIGHTS OF PRESCRIBING INFORMATION” page that directs to the indication under “1. INDICATIONS AND USAGE” of the “FULL PRESCRIBING INFORMATION”.<sup>269</sup>



<sup>266</sup> Rajeev Saggar Dep. Tr. at 196:17-197:22; *supra* §§ III.C, IV.A.1, IV.A.2.a-b.

<sup>267</sup> Rajeev Saggar Dep. Tr. at 212:5-213:1; *supra* §§ III.C, IV.A.1, IV.A.2.a-b.

<sup>268</sup> *Supra* § IV.A.2.a; Yutrepia PH-ILD sNDA (LIQ\_PH-ILD\_00091023) at -023-024; Amendment Cover Letter (LIQ\_PH-ILD\_00091022) at -022; Amended Proposed Label (LIQ\_PH-ILD\_00091129) at -129-130, -139-142.

<sup>269</sup> Compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021 with Amended Proposed Label (LIQ\_PH-ILD\_00091129) at -129-130; *supra* § IV.A.1.

## **1.2 Pulmonary Hypertension Associated with ILD**

YUTREPIA is indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%) [see *Clinical Studies (14.2)*].

These indications are essentially indistinguishable to those recited in the Tyvaso labels with the Tyvaso labels instead reciting “[t]he study with Tyvaso establishing effectiveness” and the indication under 1.2 beginning “Tyvaso is indicated” and “Tyvaso DPI is indicated.”<sup>270</sup> And the etiology breakdown is consistent with those subpopulations in the INCREASE study.<sup>271</sup> Moreover, the indication provided under Section 1.2 directs to final material that Liquidia added to the label on July 24, 2023 under “14 CLINICAL STUDIES”: “14.2 Pulmonary Hypertension Associated with ILD (WHO Group 3).”<sup>272</sup>

150. Section 14.2 imports the corresponding language from the Tyvaso labels.<sup>273</sup> This language provides a general description of the INCREASE study—“a 16-week, randomized, double-blind, placebo-controlled, multicenter study that enrolled 326 patients with PH-ILD.”<sup>274</sup>

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<sup>270</sup> Compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021 with 2022 Tyvaso Label (UTC\_PH-ILD\_005268) at -268-269 and 2022 Tyvaso DPI Label (UTC\_PH-ILD\_010709) at -709-710; see also Rajeev Saggar Dep. Tr. at 84:3-19.

<sup>271</sup> Compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021, -031 with INCREASE publication (UTC\_PH-ILD\_010790) at -795; see also Rajeev Saggar Dep. Tr. at 85:12-22 (Q. The patient population For Tyvaso and Tyvaso DPI and Yutrepia is all the same set of PH-ILD patients, correct? A. Yeah, so it specifies the specific subgroups of patients with interstitial lung disease and combined pulmonary fibrosis with emphysema, various percentages, that were part of the study that was used which was increased, correct.); *supra* § IV.A.1.

<sup>272</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021; Compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031-033 with Amended Proposed Label (LIQ\_PH-ILD\_00091129) at -139-142; *supra* § IV.A.1.

<sup>273</sup> Compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031-033 with 2022 Tyvaso Label (UTC\_PH-ILD\_005268) at -278-281 and 2022 Tyvaso DPI Label (UTC\_PH-ILD\_010709) at -719-722.

<sup>274</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031; *supra* § III.D.2.

INCREASE was a 16-week, randomized, double-blind, placebo-controlled, multicenter study that enrolled 326 patients with PH-ILD. Enrolled study patients predominately had etiologies of idiopathic interstitial pneumonia (45%) inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema (25%), and WHO Group 3 connective tissue disease (22%). The mean baseline 6MWD was 260 meters.

This following added language provides the contours of the INCREASE study's dosing regimen:<sup>275</sup>

Patients in the INCREASE study were randomized (1:1) to either placebo or treprostinil inhalation solution in four daily treatment sessions with a target dose of 9 breaths (equivalent to 79.5 mcg YUTREPIA) per session and a maximum dose of 12 breaths (equivalent to 106 mcg YUTREPIA) per session over the course of the 16-week study. Approximately 75% of patients randomized to treprostinil inhalation solution titrated up to a dose of 9 breaths, 4 times daily or greater, with 48% of patients randomized to treprostinil inhalation solution reaching a dose of 12 breaths, 4 times daily during the study. The primary efficacy endpoint was the change in

These instructions convert the INCREASE study's target dose of 9 breaths QID and maximum dose of 12 breaths QID to Yutrepia capsule doses that these instructions state are equivalent: 79.5µg and 106 µg, respectively.<sup>276</sup> This language further indicates that the subjects in the INCREASE treatment arm were titrated to these doses over the course 16-weeks with approximately 75% of subjects reaching INCREASE's target dose and 48% of subjects reaching INCREASE's maximum dose.<sup>277</sup>

151. As discussed further below, this added language also reports 6MWD and clinical worsening due to interstitial lung disease data that was generated from the INCREASE study.<sup>278</sup>

<sup>275</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031; *supra* § III.D.2.

<sup>276</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031; *supra* §§ III.D.2, IV.A.2.b (The doses that were used in LTI-102 to demonstrate Yutrepia's biocomparability to Tyvaso were Tyvaso at 9 breaths QID (i.e., the INCREASE study's target dose) and a 79.5µg Yutrepia capsule.).

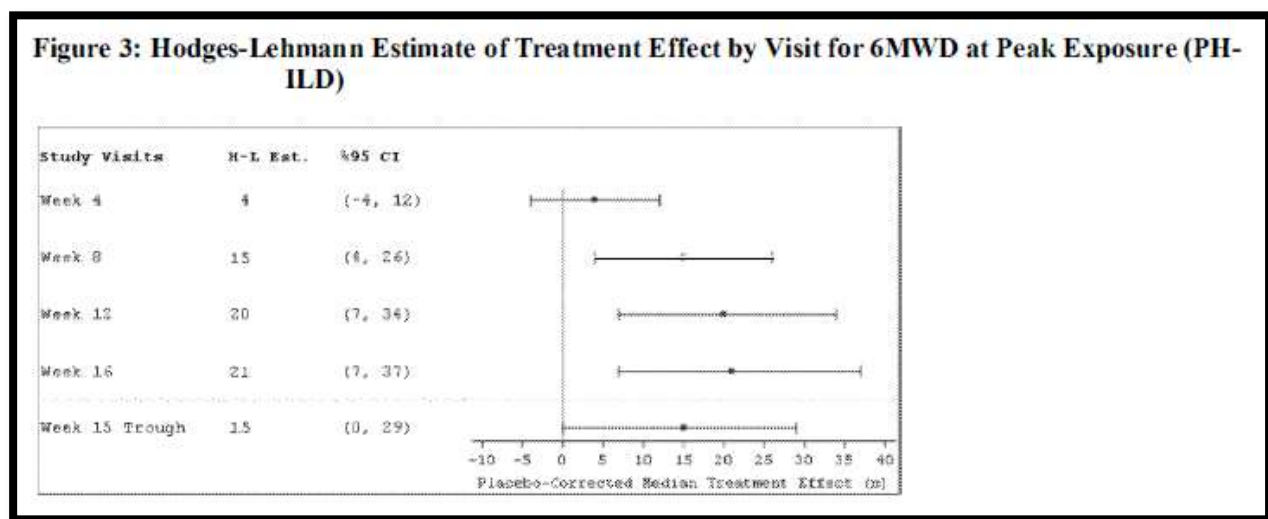
<sup>277</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031; *supra* § III.D.2.

<sup>278</sup> *Infra* § IV.A.3.a-b; *see also* Rajeev Saggarr Dep. Tr. at 84:24 - 85:1 ("It relies on -- the label -- the label has specific results, such as exercise capacity, that are embedded in the label.").

152. All these amendments remain unchanged in the tentatively approved Yutrepia label.<sup>279</sup>

**a. 6MWD**

153. As noted above, the amendments to the Yutrepia label added 6MWD data generated from the INCREASE study.<sup>280</sup> This language correctly notes that the INCREASE study’s “primary efficacy endpoint was the change in 6MWD measured at peak exposure (between 10 and 60 minutes after dosing) from baseline to Week 16.”<sup>281</sup> This language also reflects that subjects administered Tyvaso exhibited a placebo-corrected median change from baseline in peak 6MWD of 21 meters at Week 16 ( $p=0.004$ ) using Hodges-Lehmann estimate.<sup>282</sup> These data are graphically represented by Figure 3 of the Yutrepia label:<sup>283</sup>



<sup>279</sup> Compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021, -031-033 with Amended Proposed Label (LIQ\_PH-ILD\_00091129) at -129-130, -139-142.

<sup>280</sup> Compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031-032 with Amended Proposed Label (LIQ\_PH-ILD\_00091129) at -139-140; *supra* §§ III.D.2, IV.A.3.

<sup>281</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031; *supra* § III.D.2.

<sup>282</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031; *supra* § III.D.2.

<sup>283</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -032; *supra* § III.D.2. The same Hodges-Lehmann Estimate data for 6MWD is reported in Figure 8 of the '327 patent.

This chart also provides data regarding subjects' peak 6MWD at weeks 8 and 12 with administration of inhaled treprostinil resulting in a placebo-corrected median change from baseline of 15 and 20 meters, respectively.<sup>284</sup> Moreover, the 95% confidence intervals do not cross zero,<sup>285</sup> and thus indicate that administering inhaled treprostinil according to the INCREASE study achieved statistical significance at 8, 12, and 16 weeks with respect to 6MWD.

154. The Yutrepia label also details the INCREASE study's reported statistically significant treatment effect with respect to 6MWD after administering inhaled treprostinil for 16 weeks using the Hodges-Lehmann estimate, stating that "[p]atients receiving treprostinil inhalation solution had a placebo-corrected median change from baseline in peak 6MWD of 21 meters at Week 16 ( $p=0.004$ ) using Hodges[-]Lehmann estimate (Figure 3)."<sup>286</sup>

155. The Yutrepia label also provides a forest plot that displays the "Overall" 6MWD treatment effect after administering inhaled treprostinil for 16 weeks relative to certain subgroups of the following categories: "Age Group," "Sex," "PH-ILD Etiology," "Baseline 6MWD Category," "Baseline PVR Category," and "Maximum Study Drug Dose").<sup>287</sup> This plot provided p-values as well as 95% confidence intervals, and is reproduced here:<sup>288</sup>

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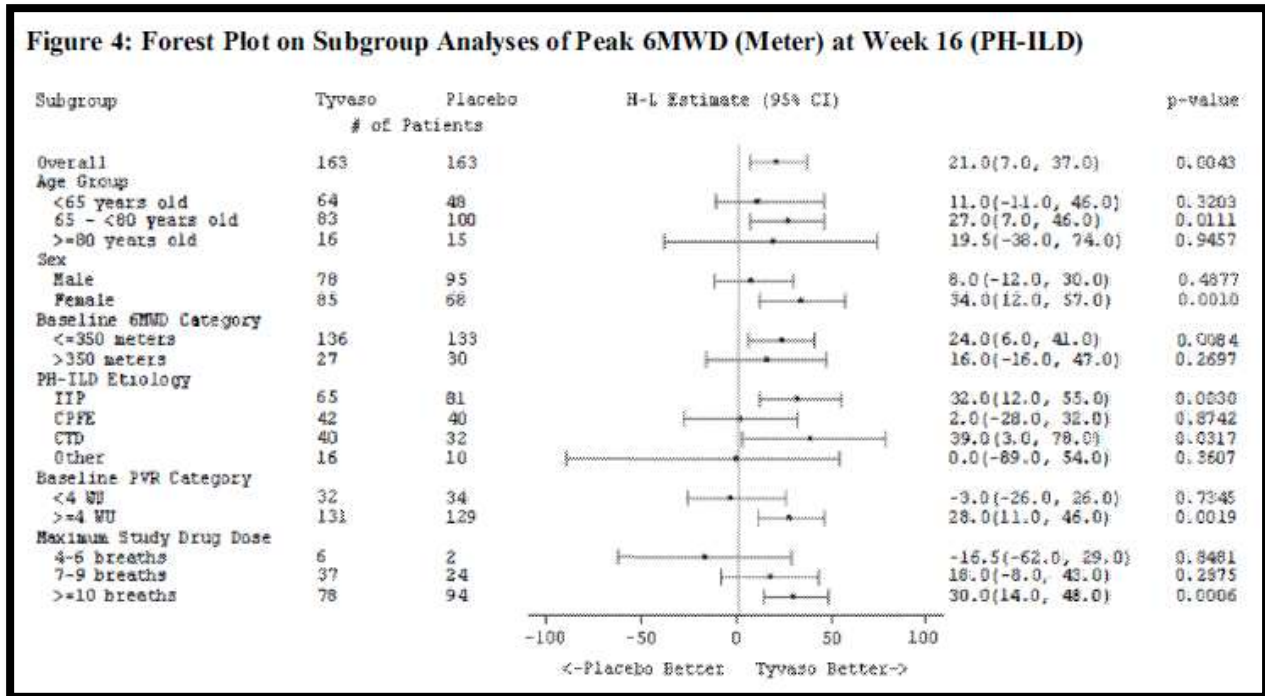
<sup>284</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -032; *supra* § III.D.2.

<sup>285</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -032; *supra* § III.D.2.

<sup>286</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031; *supra* § III.D.2.

<sup>287</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -032; *supra* § III.D.2.

<sup>288</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -032; *supra* § III.D.2.



## b. Clinical worsening events

156. As noted above, the amendments to the Yutrepia label added clinical worsening event data generated from the INCREASE study.<sup>289</sup> The Yutrepia Label indicates that the INCREASE study defines time to clinical worsening to include “hospitalization due to a cardiopulmonary indication,” “decrease in 6MWD > 15% from baseline,” “death (all causes),” or “lung transplantation.”<sup>290</sup>

157. The Yutrepia Label explicitly references the INCREASE study’s clinical worsening event data, including the statistically significant treatment effect with respect to reducing the risk of a clinical worsening event that was reported by the INCREASE study.<sup>291</sup> The Yutrepia label evidences this at least by log-rank test data, stating that “treatment with treprostinil

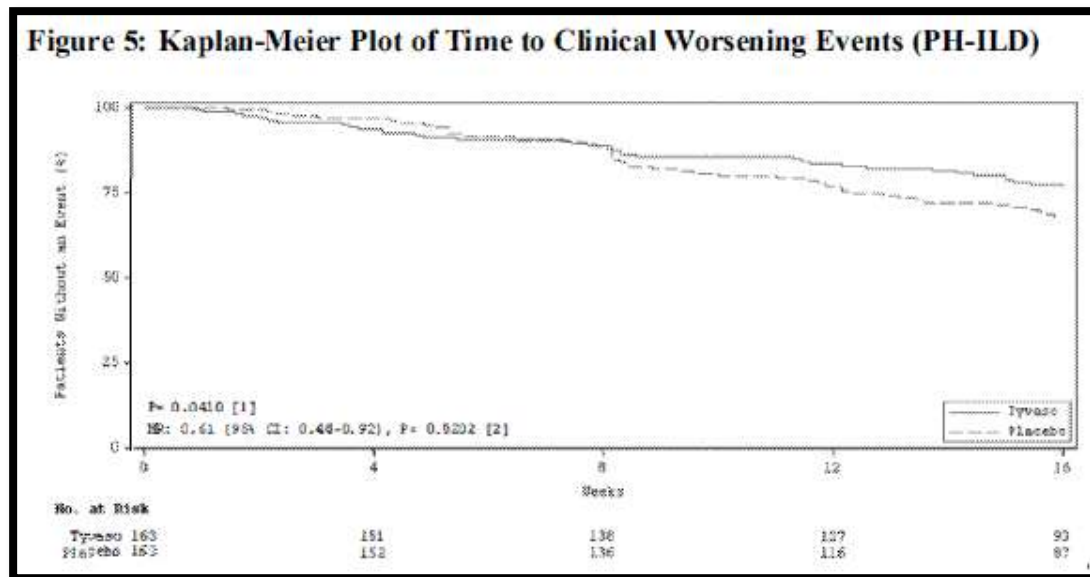
<sup>289</sup> Compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -032-033 with Amended Proposed Label (LIQ\_PH-ILD\_00091129) at -140-142; *supra* §§ III.D.2, IV.A.2.a.

<sup>290</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -032; *supra* § III.D.2.

<sup>291</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -032-033; *supra* § III.D.2.

inhalation solution demonstrated a statistically significant increase in the time to first clinical worsening event (log-rank test  $p=0.041$ ; Figure 5), and a 39% overall reduction in the risk of a clinical worsening event ( $HR=0.61$  [95% CI: 0.40, 0.92]; Figure 5).”<sup>292</sup>

158. Figure 5 of the Yutrepia Label—which presents the same data as Figure S5 of the INCREASE publication—is provided below:<sup>293</sup>



The Yutrepia Label also reports the following tables that further analyze the frequency of clinical worsening events in the INCREASE Study’s treatment and placebo arms:<sup>294</sup>

<sup>292</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -032-033; *supra* § III.D.2.

<sup>293</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -033; *supra* § III.D.2. The same Kaplan-Meier plot of time to first clinical worsening event is reported in Figure 1 of the ’327 patent.

<sup>294</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -033; *supra* § III.D.2.

**Table 3: Clinical Worsening Events (PH-ILD)**

		Tyvaso n=163 n (%)	Placebo n=163 n (%)	HR (95% CI)
<b>Clinical worsening</b>		37 (22.7%)	54 (33.1%)	0.61 (0.40, 0.92)
<b>First contributing event</b>	<b>Hospitalization due to a cardiopulmonary indication</b>	18 (11.0%)	24 (14.7%)	
	<b>Decrease in 6MWD &gt;15% from baseline directly related to PH-ILD</b>	13 (8.0%)	26 (16.0%)	
	<b>Death (all causes)</b>	4 (2.5%)	4 (2.5%)	
	<b>Lung transplantation</b>	2 (1.2%)	0	

		Tyvaso n=163 n (%)	Placebo n=163 n (%)	HR (95% CI)
<b>First of each event</b>	<b>Hospitalization due to a cardiopulmonary indication</b>	21 (12.9)	30 (18.4%)	
	<b>Decrease in 6MWD &gt;15% from baseline directly related to PH-ILD</b>	16 (9.8%)	31 (19.0%)	
	<b>Death (all causes)</b>	8 (4.9%)	10 (6.1%)	
	<b>Lung transplantation</b>	2 (1.2%)	1 (0.6%)	

**B. Liquidia's statements regarding Yutrepia's performance in PH-ILD subjects invoke INCREASE data**

159. As detailed above, Liquidia represents to FDA that its Yutrepia product is safe and effective.<sup>295</sup> And Liquidia's CMO Dr. Rajeev Saggar confirmed that Liquidia is not changing the formulation for Yutrepia, not changing its dry powder inhaler, and not changing anything that

<sup>295</sup> *Supra* § IV.A.2; Rajeev Saggar Dep. Tr. at 213:14-22. (Q. Well, I mean, I'm asking -- you are talking -- you have told FDA, right, that you think Yutrepia is going to be safe and effective for PH-ILD patients, right? A. Yes. We have told them that, and based on the tentative approval, I believe they agree with us.).

would require an update to Yutrepia's tentatively approved label.<sup>296</sup> Additionally, Liquidia's CMO confirmed that Liquidia is targeting the same PH-ILD patients for which Tyvaso or Tyvaso DPI are or can be prescribed.<sup>297</sup>

160. Liquidia's CMO explained that Yutrepia does not "chang[e] how the [treprostinil] molecule acts."<sup>298</sup> However, according to Liquidia's CMO, Yutrepia's formulation provides "the ability for the [treprostinil] molecule to act how the [treprostinil] molecule should act."<sup>299</sup> This formulation taken together with Yutrepia's dry powder inhaler is the "combination" that Liquidia's CMO purports will be easier for patients, especially PH-ILD patients, to tolerate.<sup>300</sup> Liquidia's CMO reasoned that "if [patients] can tolerate it better, they can titrate it to effective doses; and therefore, their compliance will be better; therefore, their outcomes, you know, if that occurs, will be improved."<sup>301</sup> Also, Liquidia's CMO testified that he "absolutely" believes that Yutrepia would be just as effective as Tyvaso for PH-ILD patients and that he believes Yutrepia would "meet or

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<sup>296</sup> Rajeev Saggar Dep. Tr. at 100:19-101:19 (Q. Yeah. So when you say that Liquidia is continuing to develop, are you changing -- is Liquidia changing the formulation for Yutrepia or LIQ 861? A. Not that I believe we are. Q. Okay. Is Liquidia changing the dry powder inhaler? A. No, we are not. Q. Is Liquidia changing anything that would require updating its proposed label to FDA? A. Not that I believe so.).

<sup>297</sup> Rajeev Saggar Dep. Tr. at 85:24-88:11 (Q. All I am trying to confirm, Doctor, is that 60,000 patients could take Tyvaso or Tyvaso DPI or Yutrepia, correct? A. I think those patients could use inhaled treprostinil if the clinician and the patient agreed to it, correct. Q. And so they could take either Tyvaso or Tyvaso DPI or Yutrepia, assuming the clinician and patient agree to it, correct? A. I believe so.).

<sup>298</sup> Rajeev Saggar Dep. Tr. at 218:16-219:12.

<sup>299</sup> Rajeev Saggar Dep. Tr. at 219:13-220:2 ("The way we're formulated, using print, our particles are not -- they're not a glomerate, so they tend not to stick; therefore, they could be maximized for delivery to lower airways, which then has a better -- you know, the ability for the molecule to act how the molecule should act.).

<sup>300</sup> Rajeev Saggar Dep. Tr. at 218:16-220:2.

<sup>301</sup> Rajeev Saggar Dep. Tr. at 219:8-12.

exceed the level of performance that the INCREASE study describes for Tyvaso in PH-ILD patients.”<sup>302</sup>

161. Liquidia’s CMO also testified that tolerance in turn permits titratability.<sup>303</sup> Liquidia’s CMO stated that “the data suggests that, as you titrate to doses higher, that can potentially offer the patient an ongoing clinical response that is better than the lower dose prior to it.”<sup>304</sup> Liquidia’s CMO acknowledges that all treprostinil molecules are titratable, but Liquidia’s CMO also shared that patients in Liquidia’s “ASCENT study have been able to be dosed to what [Liquidia] believe[s] are higher levels than traditionally used by Tyvaso nebulizer, especially in the INCREASE study in PH-ILD . . .”<sup>305</sup> A statement that by Liquidia’s CMO’s reasoning would indicate that Yutrepia is capable of meeting or exceeding the INCREASE study’s outcomes. Likewise, a March 13, 2024 Liquidia press release quotes Roger Jeffs—Liquidia’s CEO—announcing Liquidia’s goal for Yutrepia:

Once on the market, we are confident that the medical community will see firsthand that YUTREPIA has the potential to not only be the best-in-class inhaled product, but also the prostacyclin of first

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<sup>302</sup> Rajeev Saggar Dep. Tr. at 79:11-15; 213:24-215:8 (Q. So if there is a way to do -- to give Yutrepia to the same type of PH-ILD patients as were administered Tyvaso in INCREASE, do you think -- does Liquidia believe that Yutrepia's performance would meet or exceed the performance of Tyvaso in the INCREASE study? A. Yes. If the settings were exactly the same, yes, I do believe that.).

<sup>303</sup> Rajeev Saggar Dep. Tr. at 128:17-129:10 (Q. When you mentioned titrate-ability a minute ago in your answer, titrate-ability during the ASCENT study, what are you talking about? A. Well, Yutrepia, as is with every inhaled treprostinil product, is a drug where you can augment the dose if it’s tolerable. And the data suggests that, as you titrate to doses higher, that can potentially offer the patient an ongoing clinical response that is better than the lower dose prior to it. So as you know, all treprostinil molecules are titratable. They are not set at, for example, one or two fixed doses, as typical of most -- many drugs. . So Yutrepia is titratable, but so is Tyvaso, Tyvaso DPI, Remodulin, Orenitram, for example? A. All treprostinil products have the potential to be -- to titrate.)

<sup>304</sup> Rajeev Saggar Dep. Tr. at 128:22-129:1.

<sup>305</sup> Rajeev Saggar Dep. Tr. at 220:16-21.

choice given its convenient, low-effort delivery and wide dosing range enabled by our proprietary PRINT Technology.<sup>306</sup>

Liquidia has used similar language in its recent SEC filings:

We believe YUTREPIA can become the prostacyclin of first choice across the disease continuum in PAH and PH-ILD because of its convenience, low-resistance device and the ability to titrate to higher doses.<sup>307</sup>

162. Further, Liquidia's marketing materials directly rely on INCREASE data to market the efficacy of Yutrepia for the treatment of PH-ILD.<sup>308</sup> For example, Liquidia relies on the primary endpoint data from INCREASE, the increase in 6MWD resulting from the administration of inhaled treprostinil, to demonstrate the efficacy of Yutrepia.<sup>309</sup> These marketing materials, relying on the 6MWD data, thus suggest that when there is administration of Yutrepia, there will be some infringement of the '327 patent.<sup>310</sup> Some of these marketing publications go as far as providing 6MWD data broken down by endpoint<sup>311</sup>:

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<sup>306</sup> March 13, 2024 Press Release (LIQ\_PH-ILD\_00143338) at -338.

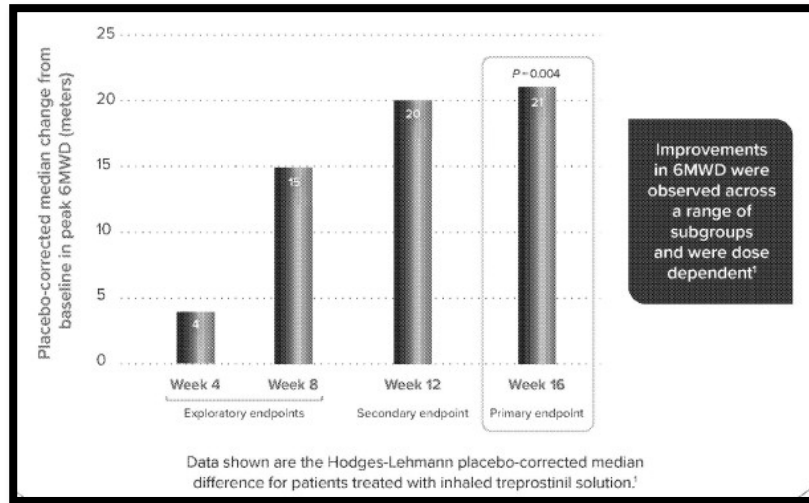
<sup>307</sup> See, e.g., 10-K 2022 at LIQ\_PH-ILD\_00141708; 10-K 2023 at LIQ\_PH-ILD\_00002016.

<sup>308</sup> See, e.g., Yutrepia Formulary Kit (LIQ\_PH-ILD\_00146970) at -977 (describing the safety and efficacy of inhaled treprostinil for the treatment of ILD using the INCREASE trial); LIQ\_PH-ILD\_00147141 (Yutrepia Marketing Handout) at -147 (describing the efficacy and safety results from the INCREASE trial); Yutrepia Presentation (LIQ\_PH-ILD\_00147196) at -235-238 (describing the efficacy results from INCREASE).

<sup>309</sup> See, e.g., LIQ\_PH-ILD\_00146936 (Yutrepia Draft Webpage 2) at LIQ\_PH-ILD00146937 ("In a clinical study, patients with PH-ILD who took an inhaled treprostinil solution walked further on average and lowered the chance of their PH-ILD worsening than those who took a placebo solution."); LIQ\_PH-ILD\_00147156 (Yutrepia Marketing Diagram) at -157 (describing the improvement in 6MWD observed in INCREASE trial patients); LIQ\_PHILD\_00146970 (Yutrepia Formulary Kit) at -977 ("Improvements in 6MWD were observed across a range of subgroups and were dose dependent"); LIQ\_PH-ILD\_00147141 (Yutrepia Marketing Handout) at -147 ("Patients treated with inhaled treprostinil solution had a significant improvement in 6MWD"); LIQ\_PH-ILD\_00147196 (Yutrepia Presentation) at -236 (showcasing the statistically significant improvement in 6MWD observed in the INCREASE trial).

<sup>310</sup> See '327 patent (UTC\_PH-ILD\_005310).

<sup>311</sup> Yutrepia Marketing Handout (LIQ\_PH-ILD\_00147141) at -147.



163. Liquidia further relies on the secondary endpoint data from the INCREASE trial, the reduction in risk of a clinical worsening event, to support Yutrepia's efficacy.<sup>312</sup> Other marketing materials reference the reduced plasma NT-proBNP levels associated with the administration of treprostinil to treat PH-ILD that were observed in the INCREASE trial as further support for Yutrepia's efficacy.<sup>313</sup> In doing so, Liquidia is again relying on INCREASE data to demonstrate why Yutrepia would also be effective for administration to the PH-ILD population. The reliance on INCREASE data, specifically that relating to the reduction in NT-proBNP levels and reduction in clinical worsening, in these marketing materials therefore suggests that administration of Yutrepia would result in infringement of the '327 patent.<sup>314</sup>

<sup>312</sup> Yutrepia Marketing Diagram (LIQ\_PH-ILD\_00147156) at -157 (describing the reduction in risk of a clinical worsening event observed in INCREASE trial patients); Yutrepia Presentation (LIQ\_PH-ILD\_00147196) at -237 ("Treatment with inhaled treprostinil solution reduced the risk of a clinical worsening event by 39%"); Yutrepia Marketing Handout (LIQ\_PH-ILD\_00147141) at -148 (describing the 39% risk reduction of a clinical worsening event seen with treatment of inhaled treprostinil in the INCREASE trial); Yutrepia Formulary Kit (LIQ\_PHILD\_00146970) at -977 (describing the lower incidence of clinical worsening observed in those patients treated with inhaled treprostinil).

<sup>313</sup> See, e.g., Yutrepia Formulary Kit (LIQ\_PHILD\_00146970) at -977 (describing the 15% reduction in NT-proBNP levels for those patients treated with inhaled treprostinil compared to a 46% increase in the placebo group).

<sup>314</sup> See '327 patent (UTC\_PH-ILD\_005310).

164. Liquidia’s Product Dossier explicitly references the finding from the INCREASE study indicating a statistically significant reduction of NT-proBNP levels after 16 weeks using MMRM applied to log-transformed NT-proBNP measurements in Section 3.1.2.

165. The table in Section 3.1.2 of the Yutrepia Product Dossier referencing NT-proBNP levels—which presents the same data as Table 2 of the INCREASE publication<sup>315</sup>—is provided below and reports a mean reduction in NT-proBNP levels of 396.35 pg/mL and p-value of  $P < 0.001$  after 16 weeks<sup>316</sup>:

<b>Secondary</b>				
<b>Endpoint</b>	<b>Inhaled treprostinil (n=163)</b>	<b>Placebo (n=163)</b>	<b>Treatment effect (95% CI)</b>	<b>P-value</b>
Change in plasma concentration of NT-proBNP from baseline to week 16 <sup>a</sup>				
Mean $\pm$ SD change, pg/mL	-396.35 $\pm$ 1904.90	1453.95 $\pm$ 7296.20	—	—
Median (range), pg/mL	-22.65 (-11,433.0 to 5373.1)	20.65 (-5483.3 to 87,148.3)	—	—
Mean $\pm$ SE ratio to baseline	0.85 $\pm$ 0.06	1.46 $\pm$ 0.11	0.58 $\pm$ 0.06 (0.47 to 0.72) <sup>b</sup>	<0.001

### C. Liquidia’s ASCENT clinical trial is informed by INCREASE

166. Liquidia is currently sponsoring a clinical trial in which Yutrepia is administered to PH-ILD subjects. The clinical trial’s official title is “An Open-Label Prospective MultiCenter Study to Evaluate Safety and Tolerability of Dry Powder Inhaled Treprostinil in Pulmonary

<sup>315</sup> *Supra* § III.D.2.b.2; INCREASE publication (UTC\_PH-ILD\_010790) at -797.

<sup>316</sup> Product Dossier (LIQ\_PH-ILD\_00146984) at -037-038. The same NT-proBNP data are reported in Table 5 of the ’327 patent (UTC\_PH-ILD\_005310).

Hypertension,” which is condensed to the acronym ASCENT (“ASCENT study”).<sup>317</sup> According to a Study Details Tab on clinicaltrials.gov, which was posted on January 31, 2024, the ASCENT study started on December 28, 2023 and “will evaluate the safety and tolerability of [Yutrepia] in subjects who have WHO Group 1 & 3 PH.”<sup>318</sup>

167. I understand that Liquidia’s CMO has testified that the ASCENT study began after Liquidia submitted its sNDA to add a PH-ILD indication to the Yutrepia label.<sup>319</sup> I further understand that Liquidia’s CMO testified that the ASCENT study has no regulatory purpose with respect to Yutrepia obtaining that PH-ILD indication and that Liquidia is conducting the ASCENT study to “showcase [Yutrepia’s] product profile.”<sup>320</sup>

168. The ASCENT study’s original Clinical Research Protocol (“ASCENT protocol”) is dated August 21, 2023,<sup>321</sup> and that protocol was amended on October 3, 2023 (“First Amended ASCENT Protocol”).<sup>322</sup> The First Amended ASCENT Protocol provides the following summary of changes:<sup>323</sup>

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<sup>317</sup> Rajeev Saggar Dep. Tr. at 101:20-102:3 (“So in your view, Liquidia is still clinically developing Yutrepia because it’s collecting data somewhere? A. Absolutely. Q. What data are you collecting right now? I assume some data from the ASCENT study; is that right? A. Yeah, we’re collecting data from the ASCENT study.”); *see also id.* at 125:20-126:24; *see generally*, LIQ\_PH-ILD\_00124867 ASCENT Protocol (LIQ\_PH-ILD\_00124867); First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607).

<sup>318</sup> ASCENT at Clinical Trials (UTC\_PH-ILD\_000395) at -395 to -396.

<sup>319</sup> Rajeev Saggar Dep. Tr. at 79:22-80:3.

<sup>320</sup> Rajeev Saggar Dep. Tr. at 80:15-81:8; *see also* Nov. 2020 LIQ861 Steering Committee Meeting (LIQ\_PH-ILD\_00113881) at -893 (Liquidia’s previous CMO, Dr. Shah, stating in November 2020 “that even beyond regulatory requirements, clinicians would want data specific to Group 3 patients, particularly in terms of safety outcomes.”)

<sup>321</sup> *See* ASCENT Protocol (LIQ\_PH-ILD\_00124867) at -867-868.

<sup>322</sup> *See* First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -607-608.

<sup>323</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -609.

SUMMARY OF AMENDMENT CHANGES		
Date of Revision	Version	Summary of Changes
03Oct 2023	1	<ul style="list-style-type: none"> <li>Replaced logo with current Liquidia logo</li> <li>Updated historical CT scan requirement from within the past 12 months to within the past 24 months in Inclusion Criteria 4.</li> <li>Provided the approximate % of patients that can be enrolled with CPFE (Inc criteria 4a) or lower mPAP according to Inclusion Criteria 4b.</li> <li>Increased the allowed window for the CT CHEST scan post administration of LIQ861 at Week 24.</li> <li>Removed statement on providing a lab manual in Section 6.4. A lab manual will not be provided as we decided to use local labs, standard of care assessments.</li> </ul>
21Aug2023	Original	Original Issue

169. I have reviewed the ASCENT protocol and the First Amended ASCENT Protocol (collectively, the “ASCENT Protocols”).<sup>324</sup> The ASCENT Protocols state that the study’s primary objective “is to evaluate the safety and tolerability of [Yutrepia] in subjects with WHO Group 1 & 3 Pulmonary Hypertension (PH).”<sup>325</sup> The ASCENT Protocols also state that the study’s “exploratory objectives . . . are to assess the effects of [Yutrepia] on exercise capacity, functional class, relevant biomarkers, and imaging assessments.”<sup>326</sup> The ASCENT Protocols contemplate multiple cohorts but to date only identify “Cohort A,” with the ASCENT Protocols characterizing this cohort as consisting of “subjects who have WHO Group 3 Pulmonary Hypertension associated with interstitial lung disease (PH-ILD)” with the First Amended ASCENT Protocol further specifying:<sup>327</sup>

<sup>324</sup> ASCENT Protocol (LIQ\_PH-ILD\_00124867) at -867-957; First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -607 to -697.

<sup>325</sup> ASCENT Protocol (LIQ\_PH-ILD\_00124867) at -871, -886; First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -611, -626.

<sup>326</sup> ASCENT Protocol (LIQ\_PH-ILD\_00124867) at -871, -886; First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -611 to -626.

<sup>327</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -626.

- Cohort A will include approximately 60 subjects who have WHO Group 3 Pulmonary Hypertension associated with interstitial lung disease (PH-ILD)
  - Approximately 20% of the cohort may include combined pulmonary fibrosis and emphysema associated ILD.
  - Approximately 10% of the total cohort may include an exploratory subset of subjects with PH-ILD meeting inclusion criteria 4b: mean pulmonary arterial pressure (mPAP) of  $\geq 21$  mmHg but  $< 30$  mmHg.

The First Amended ASCENT Protocol also provides the most up-to-date inclusion and exclusion criteria for Cohort A.<sup>328</sup>

170. According to the ASCENT Protocols, the ASCENT study is a 52-week, multi-center, open-label, single-arm study.<sup>329</sup> The ASCENT Protocols summarize the study's objectives, design, and duration as follows:<sup>330</sup>

<b>STUDY OBJECTIVES</b>	<p>The primary objective of this study is to evaluate the safety and tolerability of LIQ861 in subjects with WHO Group 1 &amp; 3 Pulmonary Hypertension (PH).</p> <p>The exploratory objectives of the study are to assess the effects of LIQ861 on exercise capacity, functional class, relevant biomarkers, and imaging assessments.</p>
<b>STUDY DESIGN &amp; DURATION</b>	<p>Study LTI-401 is an open-label, multicenter study which will evaluate the safety and tolerability of LIQ861 in subjects who have WHO Group 1 &amp; 3 PH.</p> <p>Cohort A will include approximately 60 subjects who have WHO Group 3 Pulmonary Hypertension associated with interstitial lung disease (PH-ILD)</p> <p>Additional cohorts from either Group 1 or Group 3 may be defined in future protocol amendments.</p> <p>Scheduled study visits to the clinic will occur at Screening, Baseline, Week 8, Week 16, Week 24, and Week 52 (Appendix 1). During this time, dose titration may be ordered at the Investigator's discretion and in accordance with the guidance provided in Appendix 2 and Appendix 3 (IFU).</p> <p>For subjects who complete all study assessments, upon Investigator's or subject's request, the Sponsor will continue to provide LIQ861 even after study completion until LIQ861 is approved by the regulatory authority in subject's region or its development is terminated by the Sponsor, for any reason. During the time that subjects receive LIQ861 treatment beyond the study, subjects will be asked to return to the investigative site for visits every 24 weeks (<math>\pm 14</math> days). During these visits, the study site staff will collect information on AEs and concomitant medications, will perform urine pregnancy testing (for women of child-bearing potential only) and investigational product accountability as described in Section 6.2.9.</p>

<sup>328</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -628-630.

<sup>329</sup> According to ASCENT Protocols the desired number of sites is 30. According to Study Record Version 4, there are 14 locations all of which recite "Recruiting" as their status.

<sup>330</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -611.

171. The ASCENT Protocols instruct that enrolled subjects will be placed on the following Yutrepia dosing regimen:<sup>331</sup>

**5.3. Selection of Doses in the Study**

The starting dose will be LIQ861 QID at the 26.5 µg treprostinil capsule strength. For all subjects, dosing may be titrated per instructions provided in Appendix 2. The dose of LIQ861 should be increased to  $\geq 79.5$  Treprostinil Strength by Week 4 and  $\geq 132.5$  µg Treprostinil strength by Week 15 if tolerated by the subject. If the subject is tolerating the Treprostinil dose well, doses may be increased above 132.5 µg QID but not to exceed 318 µg QID without authorization from the Sponsor. Alterations to the dosing interval (e.g., 3 times a day or 5 times a day) must be approved by the Sponsor, but the QID dosing can be titrated slower due to tolerability if the need arises. A reason for slower titration should be documented in subject's source documents and electronic case report form (eCRF).

**5.4. Timing of Dose for Each Subject**

Subjects will receive QID administration of study drug on an outpatient basis for 52 weeks or until the Sponsor decides to amend or terminate the study. For subjects who complete the study, upon Investigator's or subject's request, the Sponsor will continue to provide LIQ861 even after study completion until LIQ861 is approved by the regulatory authority in subject's region or its development is terminated by the Sponsor, for any reason.

Appendix 2, entitled GUIDANCE FOR LIQ861 DOSE SELECTION AND TITRATION, provides instructions regarding dose titration, instructing that “[a]t Baseline, the subject should initiate therapy on [Yutrepia] at the 26.5 µg treprostinil dose QID,” and should be titrated according to the provided schedule such that the subject’s dosage is “greater than or equal to 132.5µg Treprostinil strength by Week 15 if tolerated by the subject.”<sup>332</sup> Appendix 2 explains that “[t]he recommended titration schedule is based on experience in the INSPIRE study (Hill 2022) and data from INCREASE on inhaled Treprostinil (Waxman 2021).”<sup>333</sup> The schedule provides the Yutrepia “Target Dose” for each week of the 24-week trial period as well as the corresponding “Tyvaso Breath equivalents.”<sup>334</sup>

<sup>331</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -633.

<sup>332</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -665.

<sup>333</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -665.

<sup>334</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -665-666.

Week	Target Dose	Tyvaso Breath equivalents
1	26.5	$\leq 5$
2	53	$\geq 6$ and $\leq 8$
3	79.5	$\geq 9$ and $\leq 11$
4	$\geq 79.5$	$\geq 9$ and $\leq 11$
5	$\geq 106$	$\geq 12$ and $\leq 14$
6	$\geq 106$	$\geq 12$ and $\leq 14$
7	$\geq 132.5$	$\geq 15$ and $\leq 17$
8	$\geq 132.5$	$\geq 15$ and $\leq 17$
9	$\geq 132.5$	$\geq 15$ and $\leq 17$
10	$\geq 132.5$	$\geq 15$ and $\leq 17$
11	$\geq 132.5$	$\geq 15$ and $\leq 17$
12	$\geq 132.5$	$\geq 15$ and $\leq 17$
13	$\geq 159$	$\geq 18$
14	$\geq 159$	$\geq 18$
15	$\geq 159$	$\geq 18$
16	$\geq 159$	$\geq 18$
17	$\geq 159$	$\geq 18$
18	$\geq 159$	$\geq 18$
19	$\geq 185.5$	$\geq 21$
20	$\geq 185.5$	$\geq 21$
21	$\geq 185.5$	$\geq 21$
22	$\geq 185.5$	$\geq 21$
23	$\geq 185.5$	$\geq 21$
24	$\geq 185.5$	$\geq 21$

172. The dosing regimens provided in the ASCENT Protocols emphasize that investigators must consider subject tolerance when uptitrating Yutrepia, instructing that “[i]f a subject does not tolerate a higher dose, [the subject should] decrease to the previously tolerated dose, and consider if a future increase should be attempted.”<sup>335</sup> Indeed, the ASCENT Protocols

<sup>335</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -665.

instruct investigators to document if a subject's dosage does not increase between visits. Alternatively, the protocol permits investigators to increase doses above 132.5 µg QID for subjects exhibiting greater tolerance.<sup>336</sup>

173. The ASCENT Protocols' dosing regimen instructions are nearly identical to the instructions set forth in the tentatively approved Yutrepia label, which instruct treprostinil naïve patients to begin at "26.5 mcg 3 to 5 times per day" (which aligns with the initial 3 and 4 breath Tyvaso doses in the INCREASE study) and to increase their dosage by 26.5 mcg each week as tolerated (which closely tracks Tyvaso titration during INCREASE).<sup>337</sup> Moreover, the "Target Dose" to "Tyvaso Breath equivalents" in the ASCENT Protocols' recommended titration schedule seamlessly aligns with the Yutrepia's tentatively approved label's "Current Tyvaso Dose" to "YUTREPIA Dose" conversion table.<sup>338</sup> Yet the dosing regimens in the ASCENT Protocols instruct uptitrating subjects to dosages greater than or equal to 132.5 µg QID, which is contemplated by the Yutrepia label's conversion table but is greater than the Yutrepia label's 79.5-106 mcg QID "target maintenance dosage" (which respectively correspond to INCREASE study's 9-breath target dose and 12-breath maximum dose).

174. The ASCENT protocol also recognizes Yutrepia's similarity to Tyvaso dosing when it describes that:

A PK sub-study including 18 participants found that the rate of absorption of treprostinil following LIQ861 administration was similar to that following Tyvaso (Tmax of approximately 10 minutes). As expected, the elimination half-life values were similar across the LIQ861 doses and consistent with the Tyvaso doses.

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<sup>336</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -633.

<sup>337</sup> Compare ASCENT Protocol (LIQ\_PH-ILD\_00124867) at -928 to -938 and First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -668-678, with Yutrepia Label (LIQ\_PH-ILD\_00126017) at -036 to -046.

<sup>338</sup> Compare First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -665-666, with Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022.

Exposure to treprostinil increased with increasing doses of LIQ861.<sup>339</sup>

175. In view of the ASCENT study’s “exploratory objectives . . . to assess the effects of [Yutrepia] on exercise capacity, functional class, relevant biomarkers, and imaging assessments,” and express acknowledgement of the INCREASE study meeting “its primary endpoint of change in the 6-minute walk distance at 16 weeks,” the ASCENT Protocols’ dosing regimen appears designed to administer Yutrepia to enrolled PH-ILD subjects with the intended purpose and expectation of improving exercise capacity in these subjects similar to the results observed in the INCREASE study.<sup>340</sup> This is further indicated by the ASCENT study’s screening schedule including 8 and 16 week clinic visits during which 6MWD is scheduled to be assessed.<sup>341</sup> I also note that the ASCENT Study’s single-arm, open label design also indicates the ASCENT study’s acceptance of the INCREASE study as informing the expectations of the ASCENT study’s outcomes.

176. Moreover, the ASCENT Protocols provide more detail concerning the study’s exploratory endpoints:<sup>342</sup>

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<sup>339</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -625.

<sup>340</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -623, -626.

<sup>341</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -638-640.

<sup>342</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -627.

### **3.2.3. Exploratory Endpoints**

- Change in six-minute walk distance (6MWD) measured at peak exposure from Baseline to Week 8, 16, 24, and Week 52.
- Change in plasma concentration of N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) from Baseline to Week 8, 16, 24, and Week 52.
- Change in cardiac effort measured at peak exposure from Baseline to Week 8, 16, 24, and Week 52.
- Change in Computer aided Assessment of CT Chest scan from Baseline to Week 24.
- Change in Echocardiogram parameters from Baseline to Week 16
- Change in pulmonary function test from Baseline to Week 8, 16, 24, and Week 52.
- Change in WHO functional class from Baseline to Week 8, 16, 24, and Week 52.
- Change in EmPHasis 10, Dyspnea-12, and simplified cough score patient reported outcome surveys from Baseline to Week 8, 16, 24, and Week 52.

In addition to peak 6MWD being assessed after 8 and 16 weeks, the protocol also specifies that plasma concentration of NT-proBNP and pulmonary function will be assessed. According to the ASCENT Protocols, PFT includes “spirometry and Diffusion Capacity (DLCO)” and records a number of parameters as absolute values and % predicted including, FEV1, FVC, FEV1/FVC and DLCO.<sup>343</sup>

### **6.9. Pulmonary Function Test (PFT)**

A PFT including spirometry and Diffusion Capacity (DLCO) should be performed at designated study visits as defined in Appendix 1. The following parameters will be recorded (absolute values and % predicted): FEV1, FVC, FEV1/FVC and DLCO (uncorrected and corrected for hemoglobin). The site should place a deidentified scan of the PFT report in the subject file.

PFTs must be conducted after recovery from 6MWT or on a separate day. Guidance for PFT provided in Appendix 9.

### **ASCENT Protocol, § 6.9**

<sup>343</sup>ASCENT Protocol (LIQ\_PH-ILD\_00124867) at -907, -949; First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -646 to -647, -689.

#### **APPENDIX 9: PFT GUIDANCE**

For this study, it is expected that the site will follow the ATS Pulmonary Function Laboratory Management and Procedure Manual (3rd Edition) with the addition of the ATS/ERS Standardization of Spirometry Update. Predicted values should follow the Global Lung Initiative (GLI) reference equations. Spirometers measuring inspiratory and expiratory flow should be used for testing and parameters should be recorded as absolute values and % predicted. PFTs should be conducted after recovery from 6MWT.

The PFT parameters to be recorded in study source documents include:

- Forced expiratory volume in 1 second (FEV1)
- Forced vital capacity (FVC)
- Forced expiratory volume in 1 second (FEV1)/ Forced vital capacity (FVC): FEV1/FVC ratio
- Lung diffusion capacity (DLCO)

Only pre-bronchodilator values will be recorded on eCRF and will be listed. All PFT parameters and their change from baseline values will be summarized by visit.

It is clear that these endpoints parallel those of the INCREASE study.

177. Regarding statistical considerations, the ASCENT protocol indicates no formal testing is planned.<sup>344</sup> Yet the ASCENT protocol states that a formal SAP will be finalized prior to locking the study database.<sup>345</sup>

#### **8. STATISTICS**

A formal Statistical Analysis Plan (SAP), providing full details of data presentations and analyses, will be finalized prior to locking the study database. Additional statistical analyses other than those described in this section will be included in the SAP. Any deviations from the final SAP will be discussed in the final Clinical Study Report.

Nevertheless, the ASCENT Protocol reports that changes from baseline for “laboratory parameters and vital signs” as well as “exploratory endpoints” will be summarized with baseline being “the last measurement prior to the start of study treatment.”<sup>346</sup> The ASCENT protocol identifies a

<sup>344</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -616.

<sup>345</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -656.

<sup>346</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -616.

“sample size of approximately 60 subjects” including a safety population and an efficacy population for analysis.<sup>347</sup> The safety population includes all subjects receiving at least one inhalation of Yutrepia and the efficacy population includes all subjects receiving at least one inhalation of Yutrepia who also have “at least one post-dosing efficacy assessment.”<sup>348</sup> For the exploratory endpoints the protocol specifies that descriptive statistics will be used to summarize “[a]bsolute values and changes from baseline.”<sup>349</sup> Regarding safety analysis, the protocol specifies that “[t]reatment-emergent adverse events” and laboratory data such as NT-proBNP levels will be summarized.<sup>350</sup>

178. I note that because the ASCENT study is an open-label, single-arm, nonrandomized study, it cannot provide information about efficacy of Yutrepia in these subjects. Indeed, the ASCENT protocol specifically states that while efficacy endpoints identified in the INCREASE study such as changes in 6MWD, NT-proBNP, and pulmonary function will be monitored at weeks 8, 16, 24, and 52, “this study is not designed to make conclusions on efficacy.”<sup>351</sup>

179. On the other hand, the randomized and controlled INCREASE study provides information about the safety and efficacy of inhaled treprostinil in the PH-ILD subjects enrolled in the ASCENT study. The active ingredient in the ASCENT study—treprostinil—is the same active ingredient examined in the INCREASE study. Furthermore, the ASCENT study includes the same type of PH-ILD subjects that were included in the INCREASE study with very similar inclusion and exclusion criteria. The dosing schedule used in the ASCENT study also closely follows the dosing schedule followed in the INCREASE study—indeed the ASCENT Protocol

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<sup>347</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -656.

<sup>348</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -656.

<sup>349</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -656.

<sup>350</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -656-657.

<sup>351</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -627, -635.

states that the recommended titration schedule is based on data from INCREASE—and aligns with Yutrepia’s tentatively approved label. The ASCENT trial also proposes to administer PH-ILD patients even greater doses of treprostinil than administered in INCREASE. The ASCENT protocol measures many of the same data reported as endpoints of the INCREASE study. Accordingly, for largely the same reasons as I detailed above with respect to the impact of the INCREASE results,<sup>352</sup> it is my opinion that PH-ILD patients administered an inhaled treprostinil equivalent or greater to than the INCREASE study, such as patients included in the ASCENT study, will more likely than not experience the beneficial improvements reported in the INCREASE study.

## V. THE ’327 PATENT

180. U.S. Patent No. 11,826,327 titled, “Treatment for Interstitial Lung Disease” lists United Therapeutics Corporation as the applicant and assignee and Leigh Peterson, Peter Smith, and Chunqin Deng as inventors. The application leading to the ’327 patent was filed as U.S. Patent Application No. 17/233,061 on April 16, 2021. The ’327 patent lists as related applications U.S. Provisional Application No. 63/011,810 filed on April 17, 2020 and U.S. Provisional Application No. 63/160,611 filed on March 12, 2021.

181. As recited in the abstract, the ’327 patent is generally directed to:

Methods of treating of interstitial lung disease, reducing pulmonary function decline in a subject with interstitial lung disease (ILD), and increasing forced vital capacity (FVC) in a subject suffering from ILD are provided, wherein the methods include administration of treprostinil.

182. The ’327 patent contains 19 claims, with claim 1 being the only independent claim. I understand that UTC only asserts that Liquidia infringes claims 1-11 and 14-19 in this litigation. The Asserted Claims are reproduced below:

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<sup>352</sup> *Supra* § III.D.2.c.

1. A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath.
2. The method of claim 1, wherein said administering provides a statistically significant increase of a 6 minutes walk distance in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.
3. The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks of the administering.
4. The method of claim 1, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.
5. The method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.
6. The method of claim 1, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.
7. The method of claim 1, wherein said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease.
8. The method of claim 7, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.
9. The method of claim 1, wherein said administering provides a statistically significant improvement of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering.
10. The method of claim 9, wherein said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.

**11.** The method of claim 1, wherein said administering is performed by a pulsed inhalation device.

**14.** The method of claim 11, wherein the pulsed inhalation device is a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof.

**15.** The method of claim 1, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15 µg to 100 µg.

**16.** The method of claim 15, wherein the single inhalation administration event does not exceed 15 breaths by the patient.

**17.** The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks of the administering.

**18.** The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 12 weeks of the administering.

**19.** The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 16 weeks of the administering.

183. I note that much of the same clinical data reported in the INCREASE data and explicitly referenced in the proposed Yutrepia label also appears in the '327 patent as detailed below.

## **VI. ERRORS IN DR. CHANNICK'S REBUTTAL REPORT**

### **A. Dr. Channick mischaracterizes what was "already in the public domain," including the disclosure of Faria-Urbina 2018**

184. Dr. Channick asserts that "the Yutrepia™ Label is Directed to Activities in the Public Domain Long Before the '327 Patent was Filed,"<sup>353</sup> and Dr. Channick asserts that "Liquidia's Yutrepia™ label, with respect to the PH-ILD indication, as well as the accompanying dosing, is directed to what healthcare providers had already been doing to treat PH-ILD patients

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<sup>353</sup> Channick Reb. Rpt. § V.A heading; *Id.* at ¶ 46.

and was already in the public domain.”<sup>354</sup> Dr. Channick asserts that this is because “soon after approval of Tyvaso® for treatment of PAH, healthcare providers began prescribing Tyvaso® off-label using the approved PAH dosing regimen to improve exercise capacity in their PH-ILD patients” and because of public disclosures.<sup>355</sup> I disagree.

185. As detailed above, the PH-ILD indication recited in the tentatively approved Yutrepia label is as follows:<sup>356</sup>

**1.2 Pulmonary Hypertension Associated with ILD**

YUTREPIA is indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%) [*see Clinical Studies (14.2)*].

Contrary to Dr. Channick’s opinion, administering inhaled treprostinil to improve exercise capacity in PH-ILD patients was not in the public domain prior to the ’327 patent’s priority date<sup>357</sup> because there was no multicenter, randomized (1:1 inhaled treprostinil:placebo), double-blinded, placebo-controlled clinical trial until the INCREASE study, and such a study is the means by which an inhaled treprostinil treatment effect in PH-ILD patients with respect to exercise capacity could have been reliably identified and confirmed.<sup>358</sup>

186. To support his position, Dr. Channick points in part to treprostinil purportedly being prescribed to PH-ILD patients by particular individual doctors.<sup>359</sup> But as I explained in my

<sup>354</sup> Channick Reb. Rpt. ¶ 46, *see also* Channick Reb. Rpt ¶ 53, n. 54.

<sup>355</sup> Channick Reb. Rpt. ¶¶ 46-54.

<sup>356</sup> *Supra* § IV.A; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021.

<sup>357</sup> Thisted Reb. Rpt. at ¶¶ 31, 31 n.7.

<sup>358</sup> Thisted Reb. Rpt. at §§ VII, IX-XII, XV; *supra* §§ III.B, III.D.2; *e.g.*, INCREASE publication (UTC\_PH-ILD\_010790) at -790.

<sup>359</sup> Channick Reb. Rpt. ¶¶ 29, 46.

Rebuttal Report, such purported personal observations are subject to bias.<sup>360</sup> The same points that I raised in my Rebuttal Report (there in the context of validity) apply with equal force here; while I will not repeat my prior stated opinions in full, they should be considered incorporated by reference here.<sup>361</sup> Briefly, medical history is replete with examples of “treatments” widely believed to be effective—with a biologically plausible explanation that appealed to clinical intuition and seemed to be borne out by anecdotal evidence—but which ultimately turned out to be ineffective or even harmful.<sup>362</sup> Indeed, the fact that there are inevitable biases inherent in relying on clinical intuition and anecdotal evidence is central to the modern paradigm of evidence-based medicine.<sup>363</sup> As a particularly poignant example, as of 2018 there was anecdotal evidence and limited retrospective uncontrolled pilot studies suggesting that inhaled treprostinil could be safe and effective for treating patients with pulmonary hypertension associated with COPD.<sup>364</sup> However, the PH-COPD PERFECT study was the first multi-center, randomized, double-blind, placebo-controlled crossover study to test that hypothesis; it assessed inhaled treprostinil to treat PH-COPD.<sup>365</sup> But the PH-COPD PERFECT study was terminated early due to a determination by the Data and Safety Monitoring Committee that patients on the active treatment arm experienced serious adverse events at a greater rate than those receiving placebo.<sup>366</sup> Ultimately, the PH-COPD PERFECT study demonstrated that—contrary to the promising anecdotal evidence and Uncontrolled Studies that came before—administering inhaled treprostinil to patients with PH-COPD was not safe and showed no evidence of efficacy in improving 6MWD as compared to

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<sup>360</sup> Thisted Reb. Rpt. at §§VII, XII.

<sup>361</sup> Thisted Reb. Rpt. at §§ VII, IX-XII, XV; *see also supra* §§ III.B, III.D.2.c.

<sup>362</sup> *See* Thisted Reb. Rpt. at §§VII, XII.

<sup>363</sup> *See* Thisted Reb. Rpt. at §§ VII, IX.B-E, X-XII, XV; *see supra* §§ III.B, III.D.2.c.

<sup>364</sup> *See* Thisted Reb. Rpt. at §§ VII, IX.B-E, X-XII, XV; *see supra* §§ III.B, III.D.2.c.

<sup>365</sup> Thisted Reb. Rpt. at § X; *supra* § III.D.2.c.

<sup>366</sup> Thisted Reb. Rpt. at § X; *supra* § III.D.2.c.

patients receiving placebo.<sup>367</sup> Contrary to Dr. Channick's opinions, anecdotal evidence based on individual prescribers and the perceived benefits to patients is inherently biased and cannot substitute for a well-controlled clinical trial.<sup>368</sup> Accordingly, I disagree with Dr. Channick's assertion that the purported off-label prescribing practices of individual physicians would render the Asserted Claims not infringed.

187. Dr. Channick asserts that:

The method of treatment described by this indication and associated dosing of inhaled treprostinil from the Yutrepia™ label was already publicly disclosed and was in the public domain, such as [Faria-Urbina 2018 that was] published in the journal *Lung* . . . before the filing of the '327 patent.<sup>369</sup>

I disagree. Faria-Urbina 2018 fails to disclose the method described by the PH-ILD indication that is recited in the tentatively approved Yutrepia label at least for the reasons I detail above and in my Rebuttal Report: Faria-Urbina 2018 reports a small sample, retrospective, single-site, single-arm, open-label chart review that did not and cannot demonstrate any inhaled treprostinil treatment effect in PH-ILD patients.<sup>370</sup> Moreover, the data reported by Faria-Urbina 2018 lack generalizability due selection and the small sample size of PH-ILD patients and are unreliable due to severe biases, especially selection bias.<sup>371</sup> Accordingly, Faria-Urbina 2018 did not place the PH-ILD indication recited in the tentatively approved Yutrepia label, or the corresponding methods of administering inhaled treprostinil to achieve improved exercise capacity in PH-ILD patients, in the public domain.<sup>372</sup>

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<sup>367</sup> Thisted Reb. Rpt. at § X; *supra* § III.D.2.c.

<sup>368</sup> See Thisted Reb. Rpt. at §§ VII, IX.B-E, X-XII, XV; *see supra* §§ III.B, III.D.2.c.

<sup>369</sup> Channick Reb. Rpt. ¶ 47.

<sup>370</sup> Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>371</sup> Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>372</sup> Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

188. Dr. Channick's Rebuttal Report incorporates his Opening Report's discussion of Faria-Urbina 2018 in the context of purportedly anticipating the Asserted Claims. My Rebuttal Report directly addresses why Dr. Channick's Opening Report's discussion of Faria-Urbina 2018 and the other Uncontrolled Studies is wrong, and I incorporate by reference my Rebuttal Report's discussion of all the Uncontrolled Studies, including Faria-Urbina 2018.<sup>373</sup> I also discuss above limitations of Faria-Urbina 2018 and single-arm studies like Faria-Urbina 2018 that I incorporate by reference here.<sup>374</sup>

189. I continue to take issue with how Dr. Channick interprets the impact of Faria-Urbina 2018 because he ignores the deficiencies therein.<sup>375</sup> For example, Dr. Channick asserts that "Faria-Urbina 2018 discloses using inhaled treprostinil to improve the exercise capacity of PH-ILD patients."<sup>376</sup> This is incorrect as I detailed above and in my Rebuttal Report.<sup>377</sup> Critically, the chart review reported in Faria-Urbina 2018 was retrospective and only had a treatment arm, i.e., it was not placebo-controlled and not blinded.<sup>378</sup> Therefore, the reported chart review does not and could not identify any inhaled treprostinil treatment effects in PH-ILD patients.<sup>379</sup>

190. Moreover, at least some patients that the Faria-Urbina 2018 chart review followed were on other treatments in addition to treprostinil that varied from subject to subject and were continued throughout the observation period, including the followed subjects for which 6MWD is

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<sup>373</sup> Thisted Reb. Rpt. §§ VII, IX-XI, XV.

<sup>374</sup> *Supra* §§ III.B, III.D.2.c.

<sup>375</sup> Channick Reb. Rpt. ¶ 48.

<sup>376</sup> Channick Reb. Rpt. ¶ 48.

<sup>377</sup> Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>378</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937-938, -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>379</sup> Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

reported.<sup>380</sup> Therefore any changes in exercise capacity or other parameters could not be attributed to treprostinil as opposed to the other therapies that the followed patients were taking.<sup>381</sup>

191. Also, the chart review reported by Faria-Urbina 2018 excluded higher risk patients, e.g., subjects that started on treprostinil but required additional pulmonary hypertension medications (presumably because of some worsening of their lung disease) or that were recently hospitalized.<sup>382</sup> In fact, of the 72 patients identified as receiving inhaled treprostinil, all but 22 were excluded from consideration for these or other reasons; only 14 of those 22 patients were characterized as presenting with ILD (9) or CPFE (5); and the data Faria-Urbina 2018 reports often reflects fewer patients, e.g., the 6MWD data only reflects 11 followed patients.<sup>383</sup> This indicates the chart review reported by Faria-Urbina 2018 suffered from selection bias which would overstate positive results and would lack generalizability and reproducibility as detailed in my Rebuttal Report and above.<sup>384</sup>

192. Dr. Channick's Rebuttal Report—like Dr. Channick's Opening Report—completely ignores the significant limitations that the authors of Faria-Urbina 2018 themselves raise regarding the reported chart review.<sup>385</sup> I discuss this in detail in my Rebuttal Report.<sup>386</sup> For example, the authors of Faria-Urbina 2018 acknowledge the following limitations:<sup>387</sup>

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<sup>380</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937, -940; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>381</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937, -940; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>382</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937-938; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>383</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937-938; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>384</sup> Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>385</sup> Channick Reb. Rpt. § V.A.

<sup>386</sup> Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV.

<sup>387</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

### Limitations

This study is limited by its retrospective, single-center, observational, uncontrolled design. Results should be interpreted carefully in view of the small sample size and the heterogeneity of the population (COPD, ILD, and CPFE).

Dr. Channick's Rebuttal Report does not address this.<sup>388</sup> The authors of Faria-Urbina 2018 conclude that "[t]he *potential* role of inhaled *PH-specific drugs* in *Group 3 PH* should be further assessed in larger prospective studies."<sup>389</sup> First, this conclusion does not specifically identify treprostinil, PH-ILD, or assessing improved exercise capacity.<sup>390</sup> Second, this conclusion calls for further study, specifically "larger prospective studies."<sup>391</sup> In so doing, the authors acknowledge that their chart review is a small selection of patients retrospectively identified and conclude only that inhaled treprostinil is safe in Group 3 PH patients and recommend only that large prospective studies should be conducted.<sup>392</sup> Moreover, the Faria-Urbina 2018 authors warn that inhaled treprostinil's "use in *Group 3 PH* should be cautiously evaluated in specialized PH Centers, after an individualized assessment and risk-benefit consideration."<sup>393</sup> Again, the authors do not specify PH-ILD or mention improved exercise capacity.<sup>394</sup>

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<sup>388</sup> Channick Reb. Rpt. § V.A.

<sup>389</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -941 (emphasis added); Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>390</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>391</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>392</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>393</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -941 (emphasis added); Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>394</sup> Faria-Urbina 2018 ((UTC\_PH-ILD\_009936) at -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

193. I also disagree with Dr. Channick's characterization of Faria-Urbina 2018 as "disclos[ing] using inhaled treprostinil to improve the exercise capacity of PH-ILD patients" because the Faria-Urbina 2018 does not indicate that any of the 72 referenced patients were being treated with inhaled treprostinil in order to improve their exercise capacity.<sup>395</sup> Faria-Urbina 2018 reports a retrospective chart review of patients who happened to have been treated with inhaled treprostinil "based on medical judgment."<sup>396</sup> There is no indication that these followed patients were initiated on inhaled treprostinil in order to improve exercise capacity.<sup>397</sup> Indeed, if improving exercise capacity had been the goal for the 22 followed patients, it is curious that 6MWD was only monitored in 11 of the followed patients.<sup>398</sup> Also, if the Faria-Urbina 2018 authors actually believed that their publication "discloses using inhaled treprostinil to improve the exercise capacity of PH-ILD patients" as Dr. Channick asserts,<sup>399</sup> it is also curious that no such statement appears among the authors' conclusions beyond that "iTre improved WHO-FC and 6MWT distance,"<sup>400</sup> and "[t]he results suggest that iTre is safe in patients with Group 3 PH and evidence of pulmonary vascular remodeling in terms of functional class, gas exchange, and exercise capacity."<sup>401</sup> Moreover, as noted above, the authors make no conclusions concerning a specific role for inhaled PH-specific drugs in Group 3 PH, much less conclusions concerning PH-ILD patients, only

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<sup>395</sup> Channick Reb. Rpt. ¶ 48; Faria-Urbina 2018 ((UTC\_PH-ILD\_009936) at -936-941.

<sup>396</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>397</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936-941.

<sup>398</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -938-940; *see also* Faria-Urbina 2018 Suppl. Materials (UTC\_PH-ILD\_219375) at -377-378 (Of the 6 PH-ILD patients with 6MWD follow up, 3 had ILD and another 3 had CPFE).

<sup>399</sup> Channick Reb. Rpt. ¶ 48.

<sup>400</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936, -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>401</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

proposing that “[t]he potential role of inhaled PH-specific drugs in Group 3 PH should be further assessed in larger prospective studies.”<sup>402</sup>

194. Dr. Channick further asserts that:

[t]he authors of [Faria-Urbina 2018] reported a statistically “significant improvement in . . . 6-min walk distance (n=11, 243±106 vs. 308±109; p=0.022)” and concluded that, for “patients with Group 3 PH treated with [inhaled treprostinil,] ... therapy with [inhaled treprostinil] significantly improved WHO-FC and 6MWT distance.”<sup>403</sup>

First, I note that the 6MWD figures that Dr. Channick is referencing are mere change scores, which as discussed above and in my Rebuttal Report cannot be used to draw inferences about treatment effectiveness.<sup>404</sup> Second, none of what Dr. Channick cites concerns PH-ILD patients specifically, which is what claim 1 of the ’327 patent and the PH-ILD indication recited in the tentatively approved Yutrepia label are directed to.<sup>405</sup> Rather the 6MWD figures and statement cited by Dr. Channick only concern the heterogenous Group 3 population, which the Faria-Urbina 2018 authors expressly call out as a limitation of the reported chart review.<sup>406</sup> Indeed, as discussed in my Rebuttal Report, the Faria-Urbina 2018 authors acknowledged that the heterogeneous population was a limitation and accordingly cautioned readers that the “[r]esults should be interpreted carefully.”<sup>407</sup> As I discussed in my Rebuttal Report, the authors appear to offer a counterpoint to this heterogeneity limitation, acknowledging subanalyses of the COPD, ILD, and CPFE subgroups

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<sup>402</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936, -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>403</sup> Channick Reb. Rpt. ¶ 48.

<sup>404</sup> Thisted Reb. Rpt. §§ VII, IX, XI, XV; *supra* §§ III.B, III.D.2.c.

<sup>405</sup> Channick Reb. Rpt. ¶ 48; ’327 patent (UTC\_PH-ILD\_005310) at Claim 1; Yurtepia Label (LIQ\_PH-ILD\_00126017) at -020-021.

<sup>406</sup> Channick Reb. Rpt. ¶ 48; Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936, -938-941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>407</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

that only demonstrated “tendenc[ies] for improved functional class and 6-min walk distance.”<sup>408</sup> As noted in my Rebuttal Report, this is the authors reporting that these subanalyses at most indicate a “tendency” with respect to improved functional class and 6MWD when the constituent diagnoses of Group 3 PH are considered individually.<sup>409</sup> Dr. Channick’s “significant improvement” and “significantly improved” apply only to the heterogeneous aggregate population, not to PH-ILD.<sup>410</sup> Moreover, the Faria-Urbina authors state that “COPD patients tended to have greater benefit from iTre treatment” for 6MWD.<sup>411</sup> Accordingly, these aspects of Faria-Urbina 2018 that Dr. Channick cites in his Rebuttal Report do not supply evidence that the claimed methods or the PH-ILD indication recited in the tentatively approved Yutrepia label were or are in the public domain.

195. Dr. Channick also asserts that the chart review reported in Faria-Urbina 2018 “reflects ‘real-world’ use of Tyvaso® to treat PH-ILD patients since 2009.”<sup>412</sup> I disagree with his assertion for several reasons. First, Faria-Urbina 2018 only reports data from a single-center chart review as discussed above and in my Rebuttal Report.<sup>413</sup> All patients in the study were being treated at the Pulmonary Vascular Disease (PVD) Clinic at the Brigham and Women's Hospital (Boston, MA, USA), which Faria-Urbina 2018 characterizes as “a specialized PVD center.”<sup>414</sup> Ordinarily, I would not consider treatment at a highly specialized clinic as indicative of “real-

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<sup>408</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -941; Faria-Urbina 2018 Suppl. Materials (UTC\_PH-ILD\_219375) at -376-378; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>409</sup> Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>410</sup> *Compare* Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -941 *with* Channick Reb. Rpt. ¶ 48; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>411</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>412</sup> Channick Reb. Rpt. ¶ 48.

<sup>413</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937, -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>414</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937, -941.

world use.” One reason for this opinion is the very real possibility that the reported results were substantively influenced by factors unique to the single site, its investigators, and its patients.<sup>415</sup> Indeed, patients are often referred to specialty centers because they are able to provide access to care that is otherwise unavailable in the “real world.”<sup>416</sup>

196. Second, the administration of inhaled treprostinil was open label and the inclusion and exclusion criteria were generated and applied after the fact.<sup>417</sup> But the key inclusion criterion, namely the reasons for which patients were started on inhaled treprostinil, is undocumented in the chart review and likely varied from patient to patient.<sup>418</sup> Faria-Urbina 2018 only discloses that “medical judgment” was the basis for all 72 patients the publication references being initiated on inhaled treprostinil.<sup>419</sup> Whether these represent “real world” conditions is unknowable.

197. Third, biases associated with open-label studies can also arise throughout treatment and would be unlikely to be reflected in a patient’s chart.<sup>420</sup>

198. Fourth, the retrospectively applied selection criteria introduced significant selection effects as detailed above and in my Rebuttal Report.<sup>421</sup> As a consequence, the purported “real world” 6MWD results Faria-Urbina 2018 reports for WHO Group 3 to which Dr. Channick alludes represent only the 11 such patients who survived the selection process.<sup>422</sup> Faria-Urbina 2018

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<sup>415</sup> Thisted Reb. Rpt. §§ VII, IX-XI, XV; *supra* §§ III.B, III.D.2.c.

<sup>416</sup> Thisted Reb. Rpt. §§ VII, IX-XI, XV; *supra* §§ III.B, III.D.2.c.

<sup>417</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936-939, -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>418</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936-941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>419</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>420</sup> Thisted Reb. Rpt. §§ VII, IX-XI, XV; *supra* §§ III.B, III.D.2.c.

<sup>421</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936-941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>422</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936-941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

presents no data concerning the “real world” results from the other 61 patients started on inhaled treprostinil.<sup>423</sup> This means that even if the 72 treated patients were somehow reflective of “real world use” of inhaled treprostinil—which for the reasons outline above I dispute—the 11 patients on whom Faria-Urbina 2018 reports certainly would not.

199. There is no statistically valid reason to believe that the data reported by Faria-Urbina 2018 would be a reliable representation of the effects of administering inhaled treprostinil to general PH-ILD patients, let alone representative of the heterogenous population that the chart review followed.<sup>424</sup> And the authors of Faria-Urbina 2018, including Dr. Waxman, acknowledged this in their conclusions and statement of limitations.<sup>425</sup>

200. Dr. Channick also asserts that the chart review reported in Faria-Urbina 2018 “demonstrates that the indication in Yutrepia™’s label directed to improving exercise ability in PH-ILD Group 3 patients was already practiced in the real world by practicing healthcare providers and thus in the public domain.”<sup>426</sup> I disagree as detailed above and in my Rebuttal Report and for the reasons provided there and throughout this section.<sup>427</sup> As far as I know, and as discussed above and in my Rebuttal Report, no other publication as of when Faria-Urbina 2018 was published had demonstrated that administering inhaled treprostinil to PH-ILD yielded a treatment effect with respect to exercise capacity.<sup>428</sup> For the reasons explained above, throughout this section, and in my Rebuttal Report, Faria-Urbina 2018 is unable to demonstrate that either.<sup>429</sup> Moreover, the chart

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<sup>423</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936-941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>424</sup> Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>425</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936, -941

<sup>426</sup> Channick Reb. Rpt. ¶ 48.

<sup>427</sup> Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>428</sup> Thisted Reb. Rpt. §§ VII, IX, XI.B, XV; *supra* §§ III.B, III.D.2.c.

<sup>429</sup> Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

review reported in Faria-Urbina 2018 and the authors' conclusions are not directed to PH-ILD patients.<sup>430</sup> Instead, Faria-Urbina 2018 is directed to Group 3 PH, and further emphasizes that "COPD patients tended to have greater benefit from iTre treatment."<sup>431</sup> Also, as noted herein the authors of Faria-Urbina 2018 did not indicate that they initiated any of the 72 referenced patients on inhaled treprostinil to improve exercise, and the authors do not conclude that inhaled treprostinil improved exercise capacity in PH-ILD patients.<sup>432</sup> By contrast, the PH-ILD indication listed in the tentatively approved Yutrepia is directed exclusively to PH-ILD patients, concerns administration of inhaled treprostinil to improve exercise capacity, and requires that it is inhaled treprostinil that is improving exercise capacity.<sup>433</sup>

201. Dr. Channick quotes the inhaled treprostinil dosing regimen that Faria-Urbina 2018 reports was used with the subjects in that study, including those with Group 3 PH.<sup>434</sup> But Dr. Channick asserts that:

Similarly, for the same indication and patient population, the Yutrepia<sup>TM</sup> label recommends treprostinil dosing starting at 79.5 µg/day ("26.5 mcg 3 to 5 times per day") and increasing up to a target maintenance dose of between 318 µg/day to 424 µg/day ("79.5-106 mcg, 4 times daily").<sup>435</sup>

Dr. Channick asserts that "[t]his demonstrates that the recommended dosing in the Yutrepia<sup>TM</sup> label for PH-ILD Group 3 patients was already used in the real world by practicing healthcare

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<sup>430</sup> Faria-Urbina 2018 at UTC\_PH-ILD\_009936-009941.

<sup>431</sup> Faria-Urbina 2018 at UTC\_PH-ILD\_009936-009941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>432</sup> Faria-Urbina 2018 at UTC\_PH-ILD\_009936-009941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>433</sup> Yutrepia Label at LIQ\_PH-ILD\_00126020-021.

<sup>434</sup> Channick Reb. Rpt. ¶ 50.

<sup>435</sup> Channick Reb. Rpt. ¶ 50.

providers, outside the context of a prospective clinical trial, and thus was in the public domain.”<sup>436</sup> I disagree.

202. First, as discussed above, Faria-Urbina 2018 does not disclose the PH-ILD indication that is recited on the tentatively approved Yutrepia label (“Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability”).<sup>437</sup> That is at least because in the data in Faria-Urbina are insufficient to demonstrate any inhaled treprostinil treatment effect, let alone inhaled treprostinil causing improved exercise capacity in PH-ILD patients.<sup>438</sup> A randomized, controlled clinical trial would be required to do so. Faria-Urbina 2018 also does not disclose intending to administer treprostinil to improve exercise capacity.<sup>439</sup> Further, Faria-Urbina does not disclose methods targeting PH-ILD patients.<sup>440</sup> Rather Faria-Urbina 2018 concerns Group 3 PH and follows a heterogenous population of patients that were retrospectively selected and that include PH-COPD subjects.<sup>441</sup> This is a different patient population than the one targeted by Yutrepia’s PH-ILD indication.<sup>442</sup> Also, as noted above, the Faria-Urbina 2018 authors expressly identify the reported chart review’s patient heterogeneity as limitation to interpreting the results of the reported chart review.<sup>443</sup>

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<sup>436</sup> Channick Reb. Rpt. ¶ 50.

<sup>437</sup> LIQ\_PH-ILD\_00126017 at -020-021

<sup>438</sup> Faria-Urbina 2018 at UTC\_PH-ILD\_009936-009941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>439</sup> Faria-Urbina 2018 at UTC\_PH-ILD\_009936-009941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>440</sup> Faria-Urbina 2018 at UTC\_PH-ILD\_009936-009941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>441</sup> Faria-Urbina 2018 at UTC\_PH-ILD\_009938; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>442</sup> LIQ\_PH-ILD\_00126017 at -020-021

<sup>443</sup> Faria-Urbina 2018 at UTC\_PH-ILD\_009941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

203. Second, I again disagree with what Dr. Channick asserts Faria-Urbina 2018 demonstrates: “the recommended dosing in the Yutrepia™ label for PH-ILD Group 3 patients was already used in the real world by practicing healthcare providers, outside the context of a prospective clinical trial, and thus was in the public domain.”<sup>444</sup> I disagree that Faria-Urbina 2018 discloses dosing targeting PH-ILD patients.<sup>445</sup> As noted above, Faria-Urbina 2018 only indicates that inhaled treprostinil was initiated in the 72 referenced patients “based on medical judgment.”<sup>446</sup> No other details or explanation is disclosed, so Faria-Urbina 2018 does not disclose initiating inhaled treprostinil to improve exercise capacity.<sup>447</sup> Moreover, Faria-Urbina does not disclose PH-ILD-specific treatment, and the Faria-Urbina 2018 authors’ only emphasis regarding a particular Group 3 subtype is that “COPD patients tended to have greater benefit from iTre treatment.”<sup>448</sup> Moreover, the Faria-Urbina 2018 authors only conclude that there may be a “potential role of inhaled PH-specific drugs in Group 3 PH.”<sup>449</sup>

204. I again take issue with Dr. Channick’s “used in the real world” phrasing as explained herein.<sup>450</sup> I disagree with such a vague statement, especially considering that the data Faria-Urbina 2018 reports are not generalizable. As discussed above, Faria-Urbina 2018 reflects niche circumstances, e.g., conducted at a single, specialized center, and the reported chart review

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<sup>444</sup> Channick Reb. Rpt. ¶ 50.

<sup>445</sup> Faria-Urbina 2018 at UTC\_PH-ILD\_009936-009941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>446</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>447</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936-941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>448</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936-941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>449</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936, -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>450</sup> Channick Reb. Rpt. ¶ 50.

being based on a small number of selected patients, retrospective, and open-label only compounds existing biases.<sup>451</sup> Dr. Channick's omission of these details seems misleading, especially absent clarification that the "practicing healthcare providers" only refers to at most those at a single specialized center.<sup>452</sup> Again, there is no reason to believe any of the data reported by Faria-Urbina 2018 would be a reliable representation of the effects of administering inhaled treprostinil in PH-ILD patients, much less representative of the heterogenous population that the chart review purportedly followed.<sup>453</sup> And the authors of Faria-Urbina 2018, including Dr. Waxman, acknowledged this in their conclusions and statement of limitations.<sup>454</sup> That said, I do agree with Dr. Channick that Faria-Urbina 2018 did not report the results of a "prospective clinical trial"—a fact that I have addressed in detail in this section, above, and in my Rebuttal Report.<sup>455</sup>

205. Dr. Channick asserts that the dosing disclosed in the 2009 Tyvaso label is the same as the INCREASE study dosing regimen.<sup>456</sup> This is incorrect at least because the 2009 Tyvaso label does not instruct administering inhaled treprostinil to PH-ILD patient and only instructs a 9-breath target dose, not the INCREASE Study's 9-breath target dose and 12-breath maximum dose.<sup>457</sup> Dr. Channick further asserts that the dosing regimen reported by Faria-Urbina 2018 was the same as that used in the INCREASE study.<sup>458</sup> Because Faria-Urbina 2018 was retrospective and open label it is not possible to know if the 22 followed subjects were actually dosed according

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<sup>451</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937-938; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>452</sup> Channick Reb. Rpt. ¶ 50.

<sup>453</sup> Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>454</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>455</sup> Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>456</sup> Channick Reb. Rpt. ¶ 52.

<sup>457</sup> Compare 2009 Tyvaso Label (UTC\_PH-ILD\_010692) at -694 with INCREASE Protocol (UTC\_PH-ILD\_145360) at -470-471; *supra* § III.D.2.

<sup>458</sup> Channick Reb. Rpt. ¶ 52.

to the parameters Faria-Urbina 2018 report.<sup>459</sup> Dr. Channick also asserts that “[e]ven the current Tyvaso® label does nothing more than suggest using the dosing as Faria-Urbina 2018 in PH-ILD patients to improve their exercise capacity.”<sup>460</sup> I disagree. Faria-Urbina 2018, as discussed above, does not instruct administering inhaled treprostinil specifically to PH-ILD patients; does not demonstrate that any patients were administered inhaled treprostinil with the intent to improve exercise capacity; and cannot demonstrate that inhaled treprostinil has any treatment effect let alone improving exercise capacity.<sup>461</sup> The current Tyvaso labels do.<sup>462</sup>

206. Dr. Channick also asserts that an author of Faria-Urbina 2018, Dr. Waxman, confirmed “that the Faria-Urbina 2018 article included essentially the same patient population as the INCREASE study.”<sup>463</sup> I disagree that the patient population in Faria-Urbina 2018 and the INCREASE study are essentially the same. There are several key differences. First, the patients that were followed in Faria-Urbina 2018 included PH-COPD patients.<sup>464</sup> The INCREASE study excluded such patients.<sup>465</sup>

207. Second, the patient population on which Faria-Urbina 2018 reports excluded patients with < 3 months of followup, patients who had another PH-specific drug added within 3 months of treatment initiation, patients who underwent lung transplantation, patients who required hospitalization due to unstable lung disease within one month of treatment initiation, patients who

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<sup>459</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>460</sup> Channick Reb. Rpt. ¶ 52.

<sup>461</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936-941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>462</sup> 2022 Tyvaso Label (UTC\_PH-ILD\_005268) at -268-269; 2022 Tyvaso DPI Label (UTC\_PH-ILD\_010709) at -709-710.

<sup>463</sup> Channick Reb. Rpt. ¶ 52.

<sup>464</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937-938; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>465</sup> INCREASE Protocol (UTC\_PH-ILD\_145360) at -467-468; *supra* § III.D.2.

required extemporaneous right-heart catheterization, and patients whose baseline pulmonary function tests or right-heart catheterization results could not be reviewed.<sup>466</sup> The INCREASE study population excluded no such patients.<sup>467</sup>

208. Third, the INCREASE study had significant exclusion criteria absent from the Faria-Urbina 2018 cohort. These included having received any approved PAH therapy in the 60 days prior to randomization.<sup>468</sup>

209. Moreover, almost every difference in the design of the Faria-Urbina 2018 chart review and the INCREASE study contradicts Dr. Channick's position. The INCREASE study's randomized treatment arm consisted of 163 subjects and 130 of those subjects completed 16 weeks (i.e., nearly eight and seven times the number of all patients followed in Faria-Urbina 2018, respectively).<sup>469</sup> As discussed above, Faria-Urbina 2018 was a single-site chart review.<sup>470</sup> By contrast, the INCREASE study consisted of 93 geographically scattered study centers.<sup>471</sup> The open-label, nonrandom, and retroactive aspects of the Faria-Urbina 2018 chart review further skewed its population away from representative, and the decision to include a patient in Faria-Urbina 2018 is at least subject to the selection issues I discussed above and in my Rebuttal

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<sup>466</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937- 938; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>467</sup> INCREASE Protocol (UTC\_PH-ILD\_145360) at -467-468; *supra* § III.D.2.

<sup>468</sup> *Compare* INCREASE Protocol (UTC\_PH-ILD\_145360) at -467-468 *with* Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937- 938; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2, III.D.2.c.

<sup>469</sup> *Compare* INCREASE publication (UTC\_PH-ILD\_010790) at -794 *with* Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937-938; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2, III.D.2.c.

<sup>470</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -937; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2, III.D.2.c.

<sup>471</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -794; *supra* § III.D.2.

**Report.**<sup>472</sup> By contrast, the INCREASE study prespecified its inclusion/exclusion criteria, included randomized assignment to treatment arm, and was double-blinded, and thus was representative of a predefined patient population.<sup>473</sup>

210. Dr. Channick also states that Dr. Waxman testified that “the results you see with the original Tyvaso dosing you can get in PH-ILD with the same dosing[.]”<sup>474</sup> As far as I know, Dr. Waxman would not have been able to conclude that prior to the INCREASE study. As discussed herein, above, and in my Rebuttal Report, none of the Uncontrolled Studies were able to identify any inhaled treprostinil treatment effect within PH-ILD patients, and I note that Dr. Waxman was the senior author of Faria-Urbina 2018.<sup>475</sup> This is also why I disagree with Dr. Channick’s further assertion that “even the 2021 Tyvaso® label [and the Yutrepia label], which include[] the PH-ILD indication, do[] nothing more than suggest that healthcare providers and patients practice what was known in the public domain since 2009.”<sup>476</sup> That is because the INCREASE study was the first study capable of determining whether inhaled treprostinil had a treatment effect with respect to exercise capacity in PH-ILD patients.<sup>477</sup> Therefore, the PH-ILD indication recited in the 2021 Tyvaso and the Yutrepia labels was not known any time prior to when the INCREASE study data were unblinded.

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<sup>472</sup> Faria-Urbina 2018 (UTC\_PH-ILD\_009936) at -936-941; Thisted Reb. Rpt. §§ VII, IX.E, XI.B.4, XV; *supra* §§ III.B, III.D.2.c.

<sup>473</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -793; *supra* § III.D.2.

<sup>474</sup> Channick Reb. Rpt. ¶ 52.

<sup>475</sup> Thisted Reb. Rpt. §§ VII, IX, XI.B, XV; *supra* §§ III.B, III.D.2.c. Moreover, Dr. Waxman is the senior author of Faria-Urbina 2018, and even with his specialized expertise there is no reason to believe that Dr. Waxman would have been able to demonstrate an inhaled treprostinil treatment effect simply from his professional experience. As discussed above and in my Rebuttal Report, anecdotal evidence (for example from an individual provider’s clinical judgment) is subject to bias.

<sup>476</sup> Channick Reb. Rpt. ¶ 52; *see also id.* at ¶ 53 (Dr. Channick asserts that “[Yutrepia’s PH-ILD] indication and dosing is nothing more than what healthcare providers were practicing since at least 2009”)

<sup>477</sup> Thisted Reb. Rpt. §§ VII, IX, XI.B, XV; *supra* §§ III.B, III.D.2.c.

211. Dr. Channick also asserts that testimony from Liquidia’s CMO—Dr. Rajeev Saggar—“corroborates [Dr. Channick’s] opinion that Liquidia knew that treating PH-ILD patients with inhaled treprostinil to improve their exercise capacity was in the public domain.”<sup>478</sup> I disagree. Dr. Channick cites to a few lines from Dr. Rajeev Saggar’s explanation of the factual bases behind the following excerpted statement that Russell Schundler—Liquidia’s General Counsel, Secretary—made at the 2024 JPMorgan Healthcare Conference:<sup>479</sup>

And the other thing to keep in mind is the 327 patent. What that’s really covering is physicians treating PH-ILD patients with Tyvaso in accordance with the Tyvaso label, and doctors have been doing that for more than 10 years. Rajeev Saggar, our CMO, when he was treating patients, he was treating patients with Tyvaso -- PH-ILD patients with Tyvaso.

In particular, Dr. Channick cites to Dr. Rajeev Saggar explaining the factual basis of the second sentence: “What that’s really covering is physicians treating PH-ILD patients with Tyvaso in accordance with the Tyvaso label, and doctors have been doing that for more than 10 years.”<sup>480</sup> Dr. Rajeev Saggar testified that he supplied that factual basis based on his own purported clinical practice and what Dr. Rajeev Saggar characterized as “body of literature.”<sup>481</sup> Dr. Rajeev Saggar, however, reveals that this so-called “body of literature” consists of only two publications and one abstract: Parikh 2016, Agarwal 2015, and Faria-Urbina 2018, i.e., the inhaled treprostinil Uncontrolled Studies.<sup>482</sup> As discussed here, above, and in my Rebuttal Report, none of the chart reviews reported in Parikh 2016, Agarwal 2015, and Faria-Urbina 2018 can establish any inhaled

<sup>478</sup> Channick Reb. Rpt. ¶ 51 (citing to Rajeev Saggar Dep. Tr. at 207:10-208:14).

<sup>479</sup> Channick Reb. Rpt. ¶ 51; Rajeev Saggar Dep. Tr. at 197:25-208:16; Schundler Press Release (LIQ\_PH-ILD\_00133247) at -253.

<sup>480</sup> Channick Reb. Rpt. ¶ 51; Rajeev Saggar Dep. Tr. at 204:24-208:16.

<sup>481</sup> Rajeev Saggar Dep. Tr. at 202:14-21 (“I informed him that, of course, there’s a body of level – there’s a body of literature that has shown that Tyvaso has been used to treat PH-ILD for almost 10 years or longer. Treprostinil has been used to PH-ILD definitely longer than 10 years.”), 205:3-8, 207:10-24 (“I informed you, my personal experience with Tyvaso and PH-ILD, and I also informed you that there’s a body of evidence that’s existed in the literature for, you know, on or around 10 years using treprostinil to treat -- sorry, using Tyvaso to treat PH-ILD.”).

<sup>482</sup> Rajeev Saggar Dep. Tr. at 207:24-208:16.

treprostinil treatment effect.<sup>483</sup> Therefore, I disagree with Drs. Channick and Rajeev Saggar to the extent either takes the position that any of these chart reviews demonstrate any inhaled treprostinil treatment effect in PH-ILD. Concluding otherwise evidences a glaring misunderstanding of the fundamental principles of clinical study design, controlling for bias, and statistical analysis, and is contrary to the conclusions the authors of each report draw and the limitations they identify respectively.<sup>484</sup>

**B. Dr. Channick's attempts to disassociate Yutrepia from INCREASE's findings is misguided, ignores the Yutrepia label, and disregards the INCREASE clinical study results that Liquidia has relied upon for Yutrepia's tentative approval**

**1. Yutrepia's label only relies on the INCREASE Study to support clinical efficacy and safety of its tentatively approved pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability indication**

212. Dr. Channick asserts that the Yutrepia label is insufficient to demonstrate that healthcare providers and patients will directly infringe dependent Asserted Claims 2-10 and 17-19 of the '327 patent.<sup>485</sup> In particular, Dr. Channick argues that because the Yutrepia label describes UTC's clinical testing of Tyvaso® from the INCREASE study and not the testing of Yutrepia in any patient or study subject, the Yutrepia label cannot be used to establish infringement based on the future use of Yutrepia by physicians and patients.<sup>486</sup> In reaching this conclusion, Dr. Channick acknowledges that aspects of UTC's INCREASE study that are claimed by the dependent Asserted Claims are described in the Yutrepia label. He argues that other claimed aspects are not supported by the Yutrepia label.<sup>487</sup> Dr. Channick asserts that a POSA would not understand the Yutrepia

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<sup>483</sup> Thisted Reb. Rpt. §§ VII, IX, XI.B, XV; *supra* §§ III.B, III.D.2.c.

<sup>484</sup> *See* Thisted Reb. Rpt. §§ VII, IX, XI.B, XV; *supra* §§ III.B, III.D.2.c.

<sup>485</sup> Channick Reb. Rpt. at ¶¶ 55-56.

<sup>486</sup> *Id.* at ¶¶ 56-57.

<sup>487</sup> *Id.* at ¶ 57.

label to incorporate each of the INCREASE study's results because the Yutrepia label contains only a "limited description of certain aspects of the INCREASE study."<sup>488</sup>

213. I disagree with Dr. Channick's attempt to disassociate the results of UTC's INCREASE study from the Yutrepia label. As discussed elsewhere in this report, the INCREASE study is the only evidence provided in the tentatively approved Yutrepia label to support clinical efficacy with respect to Yutrepia's PH-ILD indication.<sup>489</sup> Therefore, Liquidia has proposed to inform physicians, other healthcare providers, and patients that it has relied entirely on the INCREASE study to characterize Yutrepia's effectiveness for treating PH-ILD. As detailed above, Liquidia was permitted to rely on FDA's prior approval of Tyvaso for the PH-ILD indication—and thus the INCREASE study—to establish the efficacy of Yutrepia in the treatment of PH-ILD because Liquidia (a) sought approval via the section 505(b)(2) pathway, and (b) established that doing so was scientifically appropriate since Tyvaso and Yutrepia share similar bioavailability.<sup>490</sup> I understand from counsel that, for the purposes of infringement, Yutrepia is therefore bound by its proposed label. In other words, when Yutrepia is administered in accordance with its proposed label to PH-ILD patients, it will perform consistent with the results of the INCREASE study, i.e., it is more likely than not that Yutrepia will exhibit the treatment effects reported by the INCREASE study when it is administered to PH-ILD patients. Likewise, I understand from counsel that for the purposes of infringement, any differences between Tyvaso and Yutrepia that Dr. Channick asserts to exist are immaterial with respect to Yutrepia's performance, as the proposed label instructs that Yutrepia's performance will be entirely consistent with that of the INCREASE study.

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<sup>488</sup> *Id.*

<sup>489</sup> *Supra* §§ IV.A.2, IV.A.3; *see also* Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031-033.

<sup>490</sup> *Supra* §§ III.C, IV.A.2.

214. I have also explained above that Liquidia has attached the results of the INCREASE study to Yutrepia because Liquidia relied solely on the INCREASE study to establish Yutrepia's effectiveness for the PH-ILD indication in seeking regulatory approval via the 505(b)(2) pathway.<sup>491</sup> I have described above that this reliance indicates that if Yutrepia were administered consistent with its tentatively approved label or if a clinical trial were conducted with Yutrepia that was similar in design and conduct as the INCREASE study, the hypothetical administration or clinical trial would be expected to produce results identical to (or nearly identical to) those generated by the INCREASE study.<sup>492</sup> Therefore, as detailed elsewhere, it is more likely than not that Yutrepia will demonstrate the same treatment effects as those demonstrated by the INCREASE study, including in the same or similar magnitudes (which I have described earlier in this report) as those demonstrated by the INCREASE study, when Yutrepia is administered according to its tentatively approved label.<sup>493</sup> Those treatment effects include improved 6MWD, reduced plasma concentration of NT-proBNP, decreased risk of exacerbations due to interstitial lung disease, decreased risk of clinical worsening events due to interstitial lung disease, and improved forced vital capacity.<sup>494</sup> Thus, it is my opinion that the Yutrepia label demonstrates that physicians and patients administering Yutrepia in accordance with the prescribing information will directly infringe the dependent Asserted Claims of the '327 patent.

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<sup>491</sup> *Supra* § III.C.

<sup>492</sup> *Supra* §§ III.C, III.D.2.c.

<sup>493</sup> *Supra* § III.C.

<sup>494</sup> *Supra* § III.D.2 (describing treatment effects and magnitudes reported by the INCREASE study).

**2. Dr. Channick ignores the scientific results on which Liquidia relied to achieve tentative approval for Yutrepia.<sup>495</sup>**

215. As noted above, Dr. Channick asserts that none of the evidence that Dr. Nathan raises in his Opening Report “involves the testing of Yutrepia™ in any patient or study subject[, and] all of this evidence is limited to the use of Tyvaso® in clinical study subjects as part of the INCREASE study.”<sup>496</sup> Yet Dr. Channick is merely describing characteristics of Liquidia’s 505(b)(2) sNDA to add a PH-ILD indication to Yutrepia—an application that completely lacks any testing of Yutrepia in any PH-ILD patient and for which all PH-ILD data is derived from the INCREASE study.<sup>497</sup> Dr. Channick nonetheless asserts that the INCREASE study’s findings “[are] not sufficient to prove that any future use of Yutrepia™ will meet all the limitations of the dependent Asserted Claims,” paradoxically grounding his position in the fact that Liquidia has pursued a PH-ILD indication for its Yutrepia product relying entirely the INCREASE study to evidence Yutrepia’s clinical efficacy in PH-ILD patients.<sup>498</sup> Moreover, Dr. Channick’s position even encompasses the Asserted Claims that address 6MWD (2-3 and 17-19) and clinical worsening

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<sup>495</sup> While technically a 505(b)(2) submission, Liquidia’s application looks very much like an ANDA. While the comparative bioavailability study required for 505(b)(2) approval is not required to demonstrate bioequivalence, Yutrepia meets the criteria for bioequivalence in both rate and extent of absorption. On the NDA-ANDA spectrum, Yutrepia falls close to the ANDA.

<sup>496</sup> Channick Reb. Rpt. at ¶ 56; .

<sup>497</sup> See *supra* §§ III.C, IV.A; Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -360-362; Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -028-030; FDA Response (LIQ\_PH-ILD\_00120424) at -424-427; Weidman Email re: Pre-sNDA Meeting (LIQ\_PH-ILD\_00148509) at -509; Rajeev Saggar Dep. Tr. at 67:20-68:13, 68:14-69:4, 70:11-72:16; 77:3-79:9; 84:24-85:1, 96:17-97:1, 195:20-197:23, 212:5-213:1.

<sup>498</sup> Channick Reb. Rpt. at ¶ 57; see *supra* §§ III.C, IV.A; Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -360-362; Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -028-030; FDA Response (LIQ\_PH-ILD\_00120424) at -424-427; Weidman Email re: Pre-sNDA Meeting (LIQ\_PH-ILD\_00148509) at -509; Rajeev Saggar Dep. Tr. at 67:20-68:13, 68:14-69:4, 70:11-72:16; 77:3-79:9; 84:24-85:1, 96:17-97:1, 195:20-197:23, 212:5-213:1.

events (7-8).<sup>499</sup> Yet Yutrepia's tentatively approved label's only recited clinical efficacy support for its PH-ILD indication is the summary of the INCREASE study, and that summary expressly describes the INCREASE study data, evidencing the statistically significant 6MWD and clinical worsening event treatment effects that the INCREASE Study reported.<sup>500</sup> In spite of the tentatively approved label's reliance on this data for its PH-ILD indication,<sup>501</sup> Dr. Channick asserts:

The approved indication on the Yutrepia<sup>TM</sup> label does not include any language pertaining to statistical significance or specific time intervals for taking measurements. It further does not mention the plasma concentration of NT-proBNP, exacerbations of ILD, clinical worsening events or forced vital capacity.<sup>502</sup>

I disagree. The tentatively approved Yutrepia label expressly reports the statistically significant treatment effects that the INCREASE study detected for 6MWD at 8, 12, and 16 weeks after initiation of inhaled treprostinil, along with the magnitude of those effects, and reports a statistically significant reduction in clinical worsening events that the INCREASE study also detected.<sup>503</sup>

216. Dr. Channick specifies that his position is that the differences that FDA found acceptable for Yutrepia to seek 505(b)(2) approval prevent the INCREASE study from evidencing "any future use of Yutrepia<sup>TM</sup> will meet all the limitations of the dependent Asserted Claims."<sup>504</sup> I disagree.

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<sup>499</sup> Channick Reb. Rpt. ¶ 55.

<sup>500</sup> *Supra* §§ III.C, III.D.2, IV.A; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031-033.

<sup>501</sup> *Supra* §§ III.C, IV.A; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031-033; Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -360-362; Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -028-030; FDA Response (LIQ\_PH-ILD\_00120424) at -424-427; Weidman Email re: Pre-sNDA Meeting (LIQ\_PH-ILD\_00148509) at -509; Rajeev Saggar Dep. Tr. at 67:20-68:13, 68:14-69:4, 70:11-72:16; 77:3-79:9; 84:24-85:1, 96:17-97:1, 195:20-197:23, 212:5-213:1.

<sup>502</sup> Channick Reb. Rpt. at ¶¶ 57-58.

<sup>503</sup> *Supra* §§ III.D.2, IV.A; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031-033; *see generally* INCREASE publication (UTC\_PH-ILD\_010790).

<sup>504</sup> Channick Reb. Rpt. at ¶ 57; *supra* § III.C.

217. First, I understand from counsel that the analysis is not concerned with “any future use of Yutrepia,”<sup>505</sup> rather the relevant use is that instructed by Yutrepia’s tentatively approved label with respect to the PH-ILD indication.<sup>506</sup>

218. Second, as detailed above, Liquidia has represented to FDA and admits that Yutrepia’s only active ingredient is treprostinil.<sup>507</sup> As I explained above, because treprostinil is Yutrepia’s only active ingredient and because Liquidia relies on INCREASE to support approval of its own product, the INCREASE study is more than sufficient evidence that administering Yutrepia to patients with PH-ILD will more likely than not exhibit the treatment effects that the INCREASE study reported.<sup>508</sup> This is because the INCREASE study’s prospective, multicenter, randomized, doubled-blinded, placebo-controlled design was able to identify that administering inhaled treprostinil to patients with PH-ILD elicited improved exercise capacity, improved 6MWD, reduced plasma NT-proBNP concentration, improved FVC, reduced risk of clinical worsening events due to interstitial lung disease, and reduced risk of exacerbations due to interstitial lung disease.<sup>509</sup> As explained above, the INCREASE study randomized a large, well-defined cohort of PH-ILD patients (326 patients that were randomized into 163-person treatment and placebo arms); carefully monitored outcomes and obtained data in a well-defined, blinded, and uniform way over

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<sup>505</sup> Channick Reb. Rpt. at ¶ 57.

<sup>506</sup> *Supra* § III.C, IV.A, Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021, -031-033.

<sup>507</sup> *Supra* § IV.A; e.g., Original NDA 213005 § 2.6.1 (LIQ\_PH-ILD\_00045498) at -500-504.

<sup>508</sup> *Supra* §§ III.D.2, IV.A; Original NDA 213005 § 2.6.1 (LIQ\_PH-ILD\_00045498) at -500-504; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -031-033 (instructing that Yutrepia 79.5µg and 106µg capsules are “equivalent” to 9 and 12 Tyvaso breaths respectively and instructing that target the maintenance dose for its PH-ILD indication is 79.5µg to 106µg capsules, QID); 2022 Tyvaso Label (UTC\_PH-ILD\_005268) at -269 (instructing that Tyvaso’s target maintenance range for its PH-ILD indication is 9 to 12 breaths QID); *see generally* INCREASE publication (UTC\_PH-ILD\_010790); *see generally* INCREASE Protocol (UTC\_PH-ILD\_145360).

<sup>509</sup> *Supra* §§ III.B, III.D.2; Thisted Reb. Rpt. §§ VII, IX, XI, XV; *see generally* INCREASE publication (UTC\_PH-ILD\_010790); *see generally* INCREASE Protocol (UTC\_PH-ILD\_145360).

a scheduled and fixed period of treatment; and rigorously compared outcomes in patients treated with inhaled treprostinil to those receiving placebo treatment.<sup>510</sup> The INCREASE study's findings are more compelling evidence of future likely performance if the inhaled product is administered consistent with the dosing regimen that the INCREASE study applied.<sup>511</sup> That is what is occurring with the Yutrepia label that instructs administering Yutrepia to PH-ILD patients consistent with the INCREASE study's dosing regimen and to a "target maintenance dosage[s]" that the tentatively approved Yutrepia label expressly characterizes as "equivalent" to the INCREASE study's target and maximum doses.<sup>512</sup> As I have described elsewhere, by reporting the INCREASE study as the only source of clinical data supporting Yutrepia's effectiveness in PH-ILD patients,<sup>513</sup> Liquidia has acknowledged that its product will provide the same clinical efficacy when it is administered in accordance with its proposed label, which requires the same dosing regimen as the INCREASE study.<sup>514</sup>

219. Third, as detailed above, Liquidia was required to demonstrate that Tyvaso and Yutrepia—products with same single active ingredient—are otherwise biocomparable as part of

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<sup>510</sup> *Supra* §§ III.B, III.D.2; Thisted Reb. Rpt. §§ VII, IX, XI, XV; *see generally* INCREASE publication (UTC\_PH-ILD\_010790); *see generally* INCREASE Protocol (UTC\_PH-ILD\_145360).

<sup>511</sup> *Supra* § III.D.2.

<sup>512</sup> *Supra* §§ III.D.2; IV.A; *e.g.*, compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -031-033 with INCREASE Protocol (UTC\_PH-ILD\_145360) at -470-471.

<sup>513</sup> *Supra* §§ III.C., IV.A; Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -360-362; Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -028-030; FDA Response (LIQ\_PH-ILD\_00120424) at -424-427; Weidman Email re: Pre-sNDA Meeting (LIQ\_PH-ILD\_00148509) at -509; Rajeev Sagar Dep. Tr. at 67:20-68:13, 68:14-69:4, 70:11-72:16; 77:3-79:9; 84:24-85:1, 96:17-97:1, 195:20-197:23, 212:5-213:1.

<sup>514</sup> *Supra* §§ III.C; III.D.2; U.S. Food & Drug Admin., Guidance for Industry: Applications Covered by Section 505(b)(2): Draft Guidance (1999) (UTC\_PH-ILD\_227310) at -314, -315; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -031-033; *see generally* INCREASE publication (UTC\_PH-ILD\_010790).

the 505(b)(2) approval pathway,<sup>515</sup> so it is odd that Dr. Channick argues that the differences between Tyvaso and Yutrepia render the INCREASE study incapable of informing the outcomes of administering Yutrepia according to its tentatively approved label.<sup>516</sup> Moreover, Liquidia has consistently represented to FDA that Tyvaso and Yutrepia products share the same active ingredient (treprostinil) and route of administration (oral inhalation) and only a differ in formulation and dosage form.<sup>517</sup> Oddly, Dr. Channick asserted in his Opening Report—contrary to Liquidia’s representations to FDA—that Yutrepia and Tyvaso differ in formulation, dosage form, and route of administration.<sup>518</sup> Dr. Channick now asserts that the products differ in “formulation and mode of delivery.”<sup>519</sup> The latter term has no regulatory significance that I am aware of.

220. Liquidia, however, has represented to FDA that Yutrepia’s formulation only differs from Tyvaso’s in terms of excipients.<sup>520</sup> As detailed above, Yutrepia consists of the following in addition to a treprostinil salt: L-leucine, polysorbate 80, sodium citrate, sodium chloride, and trehalose.<sup>521</sup> Among these, trehalose and leucine were considered novel for inhalation route of administration and levels of polysorbate 80 were greater than previously approved.<sup>522</sup> Nonetheless,

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<sup>515</sup> *Supra* §§ III.C; IV.A; e.g., FDA Response (LIQ\_PH-ILD\_00120424) at -425-427; *see generally* Roscigno 2021 (UTC\_PH-ILD\_010665); Rajeev Saggat Dep. Tr. 68:14-69:4, 220:6-15.

<sup>516</sup> Channick Reb. Rpt. at ¶¶ 56-57.

<sup>517</sup> *Supra* §§ III.C; IV.A; Pre-IND meeting (LIQ\_PH-ILD\_00046114) at -115-118 ; Original NDA 213005 § 2.6.1 (LIQ\_PH-ILD\_00045498) at -500-503.

<sup>518</sup> Channick Op. Rpt. at ¶ 41.

<sup>519</sup> Channick Reb. Rpt. at ¶ 57.

<sup>520</sup> *Supra* §§ III.C; IV.A; Original NDA 213005 § 2.6.1 (LIQ\_PH-ILD\_00045498) at -503; Original NDA 213005 § 3.2.P.4.6 (LIQ\_PH-ILD\_00062236) at -236-244.

<sup>521</sup> *Supra* §§ III.C; IV.A; Original NDA 213005 § 2.6.1 (LIQ\_PH-ILD\_00045498) at -503; Original NDA 213005 § 3.2.P.4.6 (LIQ\_PH-ILD\_00062236) at -236-244; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -026.

<sup>522</sup> *Supra* §§ III.C, IV.A; Original NDA 213005 § 2.6.1 (LIQ\_PH-ILD\_00045498) at -503; Original NDA 213005 § 3.2.P.4.6 (LIQ\_PH-ILD\_00062236) at -236-244.

Liquidia's NDA represents that its own nonclinical studies and other published literature establish the safety of Yutrepia's excipients.<sup>523</sup>

221. Otherwise, Liquidia submitted its LTI-102 data, establishing a PK bridge between Tyvaso and Yutrepia.<sup>524</sup> That study not only demonstrates that Yutrepia and Tyvaso are biocomparable (satisfying the criteria for bioequivalence) it also exemplified (together with LT1-101 data) that Yutrepia dosing and Tyvaso dosing is easily interconvertible.<sup>525</sup> Indeed such conversions feature on Yutrepia's tentatively approved label, converting the INCREASE study's target and maximum dosages into Yutrepia capsules, and the tentatively approved label states these doses are equivalent.<sup>526</sup> As detailed above, if a provider administers treprostinil to PH-ILD patients in an amount consistent with the amounts delivered in the INCREASE study, and if administering that product provides comparable bioavailability, I would expect that administration to produce efficacy results consistent with the INCREASE study.<sup>527</sup> I conclude that Yutrepia is such a product

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<sup>523</sup> *Supra* §§ III.C; IV.A; Original NDA 213005 § 2.6.1 (LIQ\_PH-ILD\_00045498) at -503; Original NDA 213005 § 3.2.P.4.6 (LIQ\_PH-ILD\_00062236) at -236-244

<sup>524</sup> *Supra* §§ III.C; IV.A; Pre-NDA meeting (LIQ\_PH-ILD\_00046156) at -163; Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; *see also* Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -360-362; *see generally* Roscigno 2021 (UTC\_PH-ILD\_010665).

<sup>525</sup> *Supra* §§ III.C; IV.A.; *see generally* Roscigno 2021 (UTC\_PH-ILD\_010665).

<sup>526</sup> *Supra* § IV.A; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -031-033 (instructing that Yutrepia 79.5µg and 106µg capsules are “equivalent” to 9 and 12 Tyvaso breaths respectively and instructing that target maintenance dose for its PH-ILD indication is 79.5µg to 106µg capsules, QID); 2022 Tyvaso Label (UTC\_PH-ILD\_005268) at -269 (instructing that Tyvaso's target maintenance range for its PH-ILD indication is 9 to 12 breaths QID).

<sup>527</sup> *Supra* §§ III.D.2, IV.A; *see generally* INCREASE publication (UTC\_PH-ILD\_010790); Yutrepia label (LIQ\_PH-ILD\_00126017) at -020-021, 031-033.

at least in view of LTI-102 and the proposed Yutrepia label.<sup>528</sup> I understand that FDA has reached a similar conclusion based on Liquidia's representations.<sup>529</sup>

222. Curiously, Dr. Channick also asserts that the following language regarding comparability of clinical trial safety data is relevant to considering the extent to which the INCREASE study informs Yutrepia efficacy outcomes in PH-ILD patients:<sup>530</sup>

**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Dr. Channick states that “in [his] opinion[] this caveat is noteworthy given the extensive differences between Yutrepia™ and Tyvaso®.”<sup>531</sup> It is not clear why Dr. Channick raises this position as it suggests that Liquidia's safety evidence for Yutrepia is insufficient.

223. Fourth, FDA concluded that, in view of the bridging studies (including Roscigno 2021), that Yutrepia could rely on the results of the INCREASE trial (because Yutrepia and Tyvaso deliver the same active ingredient using the same route of administration in comparable delivered amounts with comparable bioavailability with the same safety and tolerability profiles).<sup>532</sup> Consequently, a POSA would recognize that the results of the INCREASE trial provide a reliable guide as to clinical outcomes of inhaled treprostinil, whether Tyvaso or Yutrepia.<sup>533</sup>

<sup>528</sup> *Supra* §§ III.D.2, IV.A; *see generally* Roscigno 2021 (UTC\_PH-ILD\_010665); Yutrepia label (LIQ\_PH-ILD\_00126017) at -020-021, -031-033.

<sup>529</sup> *Supra* § IV.A; Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -028-30; FDA Response (LIQ\_PH-ILD\_00120424) at -425-427; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -017-018.

<sup>530</sup> Channick Reb. Rpt. at ¶ 10; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -023.

<sup>531</sup> Channick Reb. Rpt. at ¶ 10.

<sup>532</sup> *Supra* §§ III.C, IV.A; *see generally* Roscigno 2021 (UTC\_PH-ILD\_010665); Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -028-30; FDA Response (LIQ\_PH-ILD\_00120424) at -425-427; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -017-018.

<sup>533</sup> *Supra* §§ III.C, III.D.2, IV.A; *see generally* INCREASE publication (UTC\_PH-ILD\_010790).

224. Fifth, as detailed above, Liquidia's CMO, Rajeev Saggar, confirmed that Liquidia is not changing the formulation for Yutrepia, not changing its dry powder inhaler, not changing anything that would require an update to Yutrepia's label, and Liquidia's CMO confirmed that Liquidia is targeting the same PH-ILD patients for which Tyvaso or Tyvaso DPI are or can be prescribed.<sup>534</sup> Liquidia's CMO takes a position contrary to Dr. Channick, which is that Yutrepia's differences purportedly render Yutrepia more tolerable than Tyvaso, especially in PH-ILD patients, and Liquidia's CMO testified that Liquidia believes that increased tolerability, leads to higher titration, leads to better outcomes—than Tyvaso.<sup>535</sup> Liquidia's CMO sets the higher dosage aspect as the lynchpin.<sup>536</sup> Liquidia's CMO testified that Liquidia's ASCENT study is already observing higher dosing than observed permitted in the INCREASE study.<sup>537</sup> As noted above, Liquidia's CMO testified that he "absolutely" believes that Yutrepia would be just as effective as Tyvaso for PH-ILD patients and that he believes Yutrepia would "meet or exceed the level of performance that the INCREASE study describes for Tyvaso in PH-ILD patients."<sup>538</sup> Moreover, Liquidia's marketing materials rely on INCREASE study 6MWD data to describe the benefits of taking Yutrepia.

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<sup>534</sup> *Supra* § IV.B; Rajeev Saggar Dep. Tr. at 85:24-88:11, 100:19-101:19.

<sup>535</sup> *Supra* § IV.B; Rajeev Saggar Dep. Tr. at 128:17-129:10, 218:16-220:2.

<sup>536</sup> *Supra* § IV.B; Rajeev Saggar Dep. Tr. at 128:17-129:10, 218:16-220:2.

<sup>537</sup> *Supra* § IV.B; Rajeev Saggar Dep. Tr. at 220:16-21.

<sup>538</sup> *Supra* § IV.B; Rajeev Saggar Dep. Tr. at 79:11-15; 214:23-215:8 (Q. So if there is a way to do -- to give Yutrepia to the same type of PH-ILD patients as were administered Tyvaso in INCREASE, do you think -- does Liquidia believe that Yutrepia's performance would meet or exceed the performance of Tyvaso in the INCREASE study? A. Yes. If the settings were exactly the same, yes, I do believe that.).

225. Liquidia's CMO also testified that tolerance in turn permits titratability.<sup>539</sup> Liquidia's CMO stated that "the data suggests that, as you titrate to doses higher, that can potentially offer the patient an ongoing clinical response that is better than the lower dose prior to it."<sup>540</sup> Liquidia's CMO acknowledges that all treprostinil molecules are titratable, but Liquidia's CMO also shared that patients in Liquidia's "ASCENT study have been able to be dosed to what [Liquidia] believe[s] are higher levels than traditionally used by Tyvaso nebulizer, especially in the INCREASE study in PH-ILD . . ."<sup>541</sup> A statement that by Liquidia's CMO's reasoning would indicate that Yutrepia is capable of meeting or exceeding the INCREASE study outcomes.<sup>542</sup>

226. In view of the foregoing, Dr. Channick's position that Yutrepia's differences render administration non-infringing is wrong in view of Liquidia's representations to FDA, the INCREASE study's findings' broad implications to treprostinil products generally as well as to products that are administered consistent with the INCREASE study or are comparable to Tyvaso. Moreover, Dr. Channick's position directly conflicts with testimony from Liquidia's CMO and 30(b)(6) witness as well as Liquidia's public statements and proposed marketing materials.

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<sup>539</sup> Rajeev Saggat Dep. Tr. at 128:17-129:10 (Q. When you mentioned titrate-ability a minute ago in your answer, titrate-ability during the ASCENT study, what are you talking about? A. Well, Yutrepia, as is with every inhaled treprostinil product, is a drug where you can augment the dose if it's tolerable. And the data suggests that, as you titrate to doses higher, that can potentially offer the patient an ongoing clinical response that is better than the lower dose prior to it. So as you know, all treprostinil molecules are titratable. They are not set at, for example, one or two fixed doses, as typical of most -- many drugs. . Q. So Yutrepia is titratable, but so is Tyvaso, Tyvaso DPI, Remodulin, Orenitram, for example? A. All treprostinil products have the potential to be -- to titrate.)

<sup>540</sup> Rajeev Saggat Dep. Tr. at 128:22-129:1.

<sup>541</sup> *Supra* § IV.B; Rajeev Saggat Dep. Tr. at 220:16-21.

<sup>542</sup> *Supra* § IV.B; Rajeev Saggat Dep. Tr. at 79:11-15; 213:24-215:8.

**C. Dr. Channick overlooks how the INCREASE study, and Liquidia’s reliance on UTC’s Tyvaso label, satisfies limitations of dependent claims 2, 4, and 6-10**

227. Dr. Channick asserts that healthcare providers and patients cannot directly infringe claims 2, 4, and 6-10 for the following similar reasons:

- “Dr. Nathan provides no evidence that a healthcare provider or patient will measure any of these statistical or clinical outcomes based on the proposed Yutrepia™ label, or any of the non-label sources Dr. Nathan relies on in his report”;<sup>543</sup>
- “there is no evidence that any healthcare provider or patient would perform a statistical analysis”;<sup>544</sup>
- “Dr. Nathan points to no evidence that healthcare providers will measure statistical significance in [6MWD, plasma NT-proBNP concentration, exacerbations due to interstitial lung disease, clinical worsening events due to interstitial lung disease, or FVC] when treating patients with Yutrepia™;<sup>545</sup> and
- “Dr. Nathan’s report is devoid of any evidence showing that healthcare providers or patients perform these calculations when administering Yutrepia™.”<sup>546</sup>

I disagree with Dr. Channick that any of this evidence is required to demonstrate direct infringement of claims 2, 4, and 6-10. These seven claims are reproduced immediately below:

Asserted Claims 2, 4, and 6-10
2. The method of claim 1, wherein <i>said administering provides a statistically significant increase of a 6 minutes walk distance in the patient</i> after 8 weeks, 12 weeks, or 16 weeks of the administering.
4 .The method of claim 1, wherein <i>said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient</i> after 8 weeks, 12 weeks, or 16 weeks of the administering.
6. The method of claim 1, wherein <i>said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.</i>
7. The method of claim 1, wherein <i>said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease.</i>
8. The method of claim 7, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication

<sup>543</sup> Channick Reb. Rpt. ¶ 56.

<sup>544</sup> Channick Reb. Rpt. § V.B.1 heading.

<sup>545</sup> Channick Reb. Rpt. ¶ 62.

<sup>546</sup> Channick Reb. Rpt. ¶ 62.

and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.

9. The method of claim 1, wherein *said administering provides a statistically significant improves of forced vital capacity (FVC) in the patient* after 8 weeks, 12, weeks or 16 weeks of the administering.

10. The method of claim 9, wherein *said administering improves the forced vital capacity (FVC) in the patient* by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.

None of these claims expressly require performing statistical analyses, measuring statistical significance or outcomes, or performing calculations.

228. However, Dr. Channick takes the position that the above-listed evidence is necessary because these claims 2, 4, 6-10 “require ‘statistically significant’ results,”<sup>547</sup> specifically asserting that:

[c]laims 2, 4, 6, and 7-10 all require a “statistically significant” change in the following clinical parameters: increase in 6MWD (claim 2), a reduction in NT-proBNP plasma concentration (claim 4), exacerbations (claim 6), clinical worsening events (claims 7 and 8), and an improvement in FVC (claims 9-10).<sup>548</sup>

Moreover, Dr. Channick asserts that:

A POSA would understand that, in order to have a statistically significant change, these claims necessitate that a healthcare provider prescribe inhaled treprostinil (apply the intervention), to multiple patients (a group large enough to detect a meaningful difference), measure one of the selected parameters in each group member, aggregate the results from the patients, and then perform statistical analysis on those results.<sup>549</sup>

<sup>547</sup> Channick Reb. Rpt. ¶ 59; *id.* at ¶ 55 (Dr. Channick asserts that “each of the dependent Asserted Claims require . . . a ‘statistically significant’ result (claims 2, 4, 6, 7-8, 9-10) . . .”).

<sup>548</sup> Channick Reb. Rpt. ¶ 61; *see also id.* at ¶ 92 (Dr. Channick asserts that “Claims 2, 4, 6, and 7-10 of the ’327 patent all require that the method of treatment of claim 1 achieve ‘statistically significant’ improvements in six-minute walk distance, plasma concentration of NT-proBNP, exacerbations of interstitial lung disease, clinical worsening events, and FVC.”).

<sup>549</sup> Channick Reb. Rpt. ¶ 61; *see also id.* at ¶ 92 (Dr. Channick asserts that “to achieve an improvement in these areas and confirm its statistical significance, the person practicing the

It is also Dr. Channick's personal opinion that this "requires a healthcare provider or patient to *actively measure* whether Yutrepia™ administration produces the claimed statistically significant outcomes."<sup>550</sup> I disagree with Dr. Channick. Again, Dr. Channick is adding steps that these method claims do not recite. Moreover, what these claims recite do not require what Dr. Channick asserts is necessary for direct infringement. In particular, I disagree with Dr. Channick's characterization of these claims as requiring a physician to physically obtain clinical data for a group of patients, to perform statistical analyses on those data to determine whether the group of patients exhibit results or changes, or to obtain statistically significant results or changes in such a group.<sup>551</sup> I do not see those additional steps in the claims.

229. In claims 2, 4, 6, 7, and 9, "statistically significant" is a term embedded in a the larger phrase ("wherein *said administering provides a statistically significant*"), which is then followed by naming particular treatment effects, e.g., an "increase of a 6 minutes walk distance in the patient" (claim 2) and a "reduction of clinical worsening events due to the interstitial lung disease" (claim 7). Accordingly, I read this language as describing methods of administering inhaled treprostinil to PH-ILD patients that achieve (i.e., provide) the respective treatment effect at the population level. And those limitations are met by the INCREASE study that Liquidia's label relies upon. Although I further read claims 2, 4, and 9 as addressing those patients who exhibit the treatment effect, these three claims only require the recited inhaled treprostinil treatment effect,

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method of treatment must select a metric to measure, apply the treatment to a sufficiently large group of patients, measure the selected metric in each patient, aggregate the collected data, and perform statistical analysis on the data.").

<sup>550</sup> Channick Reb. Rpt. ¶ 62 (emphasis in original).

<sup>551</sup> Channick Reb. Rpt. ¶¶ 59, 61, 92.

not an effect of a particular magnitude. Accordingly, Dr. Channick's characterization of claims 2, 4, 6, 7, and 9 overlooks both the language of the claims and key statistical principles.

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<sup>552</sup> Deng Dep. Tr. at 161:4 – 163:19.  
<sup>553</sup> Channick Reb. Rpt. ¶¶ 61, 160, n.61, n.208, n.212.  
<sup>554</sup> Deng Dep. Tr. at 161:4-7.  
<sup>555</sup> Deng Dep. Tr. at 161:11-15.  
<sup>556</sup> Deng Dep Tr. at 161:18-22.  
<sup>557</sup> Deng Dep Tr. at 162:25 – 163:2.

231. Importantly, as [REDACTED] I detailed above, the INCREASE study has already established that administering treprostinil to PH-ILD patients provides statistically significant treatment effects with respect to 6MWD, plasma NT-proBNP concentration, risk of exacerbations due to interstitial lung disease, risk of clinical worsening events due to interstitial lung disease, and forced vital capacity.<sup>559</sup> Dr. Channick's rebuttal position regarding direct infringement of claims 2, 4, and 6-10 completely ignores this.<sup>560</sup> In view of the INCREASE study, PH-ILD patients that practice the claimed methods are more likely than not going to exhibit the treatment effects described by the INCREASE study as I detailed above, including improved 6MWD, reduced plasma concentration of NT-proBNP, decreased risk of exacerbations due to interstitial lung disease, decreased risk of clinical worsening events due to interstitial lung disease, and improved forced vital capacity.<sup>561</sup>

232. As discussed above, Liquidia has elected to rely on the INCREASE study with respect to approval of Yutrepia's PH-ILD indication.<sup>562</sup> Consequently, Liquidia has told the FDA

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<sup>558</sup> Deng Dep Tr. at 163:6-17.

<sup>559</sup> Deng Dep Tr. at 161:4 – 163:17; *supra* § III.D.2; *see generally* INCREASE publication (UTC\_PH-ILD\_010790); *see generally* Nathan 2021 (UTC\_PH-ILD\_147114).

<sup>560</sup> Channick Reb. Rpt. ¶¶ 59-63.

<sup>561</sup> *Supra* §§ III.B, III.D.2; Thisted Reb. Rpt. §§ VII, IX-XI, XV; *see generally* INCREASE publication (UTC\_PH-ILD\_010790); *see generally* INCREASE Protocol (UTC\_PH-ILD\_145360); *see generally* Nathan 2021 (UTC\_PH-ILD\_147114).

<sup>562</sup> *Supra* §§ III.C, IV.A, VI.B; Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -360-362; Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; Pre-sNDA Meeting

that the INCREASE study—and its results—describe Yutrepia, and thus the INCREASE study satisfies the respective “said administering provides a statistically significant . . .” limitations of claims 2, 4, 6, 7, and 9.<sup>563</sup> Likewise, the tentatively approved Yutrepia label exclusively refers to the INCREASE study as clinical support for the PH-ILD indication.<sup>564</sup> As discussed above, the label instructs administering Yutrepia according to the INCREASE study’s dosing regimen.<sup>565</sup> Therefore, any PH-ILD patient that is administered Yutrepia is more likely than not going to exhibit the treatment effects described by the INCREASE study as I detailed above, including improved 6MWD, reduced plasma concentration of NT-proBNP, decreased risk of exacerbations due to interstitial lung disease, decreased risk of clinical worsening events due to interstitial lung disease, and improved forced vital capacity.<sup>566</sup> Moreover, Dr. Channick is also aware that the tentatively approved Yutrepia label recites the INCREASE study statistical findings for 6MWD and clinical worsening events due to interstitial lung disease.<sup>567</sup> Yet the presence or absence of

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Request (LIQ\_PH-ILD\_00134026) at -028-030; FDA Response (LIQ\_PH-ILD\_00120424) at -424-427; Weidman Email re: Pre-sNDA Meeting (LIQ\_PH-ILD\_00148509) at -509; Rajeev Sagar Dep. Tr. at 67:20-68:13, 68:14-69:4, 70:11-72:16; 77:3-79:9; 84:24-85:1, 96:17-97:1, 195:20-197:23, 212:5-213:1.

<sup>563</sup> *Supra* §§ III.C, IV.A VI.B; Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -360-362; Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -028-030; FDA Response (LIQ\_PH-ILD\_00120424) at -424-427; Weidman Email re: Pre-sNDA Meeting (LIQ\_PH-ILD\_00148509) at -509; Rajeev Sagar Dep. Tr. at 67:20-68:13, 68:14-69:4, 70:11-72:16; 77:3-79:9; 84:24-85:1, 96:17-97:1, 195:20-197:23, 212:5-213:1; U.S. Food & Drug Admin., Guidance for Industry: Applications Covered by Section 505(b)(2): Draft Guidance (1999) (UTC\_PH-ILD\_227310) at -314, -315; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -031-033; *see generally* INCREASE publication (UTC\_PH-ILD\_010790).

<sup>564</sup> *Supra* §§ IV.A, VI.B; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021, -031-033.

<sup>565</sup> *Supra* §§ III.D.2, IV.A, IV.B, VI.B; *compare* Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -031-033 *with* INCREASE Protocol (UTC\_PH-ILD\_145360) at -470-471.

<sup>566</sup> *Supra* §§ III.D.2, IV.A, IV.B, VI.B; *compare* Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -031-033 *with* INCREASE Protocol (UTC\_PH-ILD\_145360) at -470-471; *see generally* INCREASE publication (UTC\_PH-ILD\_010790).

<sup>567</sup> *E.g.*, Channick Reb. Rpt. ¶¶ 39-38.

additional statistical data is not necessary to infringe Asserted Claims 2, 4, and 6-10 in that the Yutrepia label describes the INCREASE study's dosing regimen and 16-week duration.<sup>568</sup> The INCREASE study establishes that administering inhaled treprostinil according to the methods of the INCREASE study more likely than not provide the treatment effects recited in claims 2, 4, and 6-10.<sup>569</sup> Accordingly, in view of the Yutrepia label, the statistical inferences of the INCREASE study apply to Yutrepia.<sup>570</sup> I also, therefore, disagree with Dr. Channick's attempts to distinguish for the purposes of direct infringement of claims 2, 4, and 6-10 between the recited treatment effects that are listed on Yutrepia's label and those that are not.<sup>571</sup>

233. The INCREASE study reports the same methods of administering that the tentatively approved Yutrepia label instructs for administering Yutrepia.<sup>572</sup> The tentatively approved Yutrepia label also recites the statistical findings from the INCREASE study regarding administration of inhaled treprostinil to PH-ILD patients and the corresponding statistically significant improvement in 6MWD and reduction of clinical worsening events due to interstitial

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<sup>568</sup> See *supra* §§ III.D.2, IV.A, VI.B; see Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -031-033; see generally INCREASE publication (UTC\_PH-ILD\_010790); see generally INCREASE Protocol (UTC\_PH-ILD\_145360); see generally Nathan 2021 (UTC\_PH-ILD\_147114).

<sup>569</sup> *Supra* § III.D.2; see generally INCREASE publication (UTC\_PH-ILD\_010790); see generally INCREASE Protocol (UTC\_PH-ILD\_145360); see generally Nathan 2021 (UTC\_PH-ILD\_147114).

<sup>570</sup> *Supra* § III.D.2, IV.A, VI.B; see generally INCREASE publication (UTC\_PH-ILD\_010790); see generally INCREASE Protocol (UTC\_PH-ILD\_145360); see generally Nathan 2021 (UTC\_PH-ILD\_147114); Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -031-033.

<sup>571</sup> E.g., Channick Reb. Rpt. ¶¶ 39, 57.

<sup>572</sup> *Supra* §§ III.D.2, IV.A, VI.A; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -026-027, -031-033; see generally INCREASE publication (UTC\_PH-ILD\_010790); see generally INCREASE Protocol (UTC\_PH-ILD\_145360); see generally Nathan 2021 (UTC\_PH-ILD\_147114).

lung disease.<sup>573</sup> So, the statistical findings of the INCREASE study regarding these methods of administration would apply to Yutrepia.<sup>574</sup> Therefore, administration of Yutrepia to PH-ILD patients consistent with the tentatively approved Yutrepia label will likely yield a treatment effect consistent with the INCREASE study's findings.<sup>575</sup>

234. I see this relationship between the INCREASE study and the Yutrepia label reflected in Dr. Nathan's direct infringement positions regarding claims 2 and 7.<sup>576</sup> Dr. Nathan concludes with respect to claim 2 that:

[T]he POSA would understand that the Hodges-Lehmann estimate demonstrated statistical significance in 6MWD after weeks 8, 12, and 16 of administration. Further, the Forest Plot showed statistical significance in 6MWD, at least, at 16 weeks, and the longitudinal data analysis using mixed model repeated measurement also showed statistical significance in 6MWD over, at least, 12 and 16 weeks.. The POSA would therefore understand that the Yutrepia label discloses a statistically significant increase of a 6 minute walk distance in the PH-ILD patient after 8 weeks, 12 weeks, or 16 weeks of administration. The POSA would also understand that administration of Yutrepia to at least some PH-ILD patients would result in a similar statistically significant improvement in 6MWD as demonstrated in the Yutrepia label and the INCREASE study.<sup>577</sup>

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<sup>573</sup> *Supra* §§ III.D.2, IV.A, VI.A; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -026-027, -031-033); *see generally* INCREASE publication (UTC\_PH-ILD\_010790); *see generally* INCREASE Protocol (UTC\_PH-ILD\_145360); *see generally* Nathan 2021 (UTC\_PH-ILD\_147114).

<sup>574</sup> *Supra* §§ III.D.2, IV.A, VI.A; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -026-027, -031-033); *see generally* INCREASE publication (UTC\_PH-ILD\_010790); *see generally* INCREASE Protocol (UTC\_PH-ILD\_145360); *see generally* Nathan 2021 (UTC\_PH-ILD\_147114).

<sup>575</sup> *Supra* §§ III.D.2, IV.A, VI.A; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -026-027, -031-033); *see generally* INCREASE publication (UTC\_PH-ILD\_010790); *see generally* INCREASE Protocol (UTC\_PH-ILD\_145360); *see generally* Nathan 2021 (UTC\_PH-ILD\_147114).

<sup>576</sup> *See* Nathan Op. Rpt. ¶¶ 278, 314.

<sup>577</sup> Nathan Op. Rpt. ¶ 278.

Dr. Nathan is referring to the Hodges-Lehmann estimates cited in the Yutrepia label, which is quoting results from the INCREASE study.<sup>578</sup> I agree that the INCREASE data applies to Yutrepia and thus PH-ILD patients that are administered Yutrepia would exhibit a treatment effect consistent with INCREASE with respect to improved 6MWD.<sup>579</sup> Dr. Channick asserts that citation to peer-reviewed literature discussing the INCREASE Study is improper because “there is no reference to these publications and papers in the Yutrepia™ label nor is there any instruction or suggestion in the Yutrepia™ label to go find these materials and review them.”<sup>580</sup> Dr. Channick’s position seems odd considering that the tentatively approved label expressly references the INCREASE study, and I understand from FDA guidance that at least labels’ clinical study sections are understood to be mere summaries.<sup>581</sup> Dr. Channick’s opinions here also appear to conflict with representations Liquidia made to FDA, including that Yutrepia would rely on INCREASE data in

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<sup>578</sup> See Nathan Op. Rpt. ¶¶ 271, 278; *supra* §§ III.D.2, IV.A; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031-032; *see generally* INCREASE publication (UTC\_PH-ILD\_010790).

<sup>579</sup> See *supra* §§ III.D.2, IV.A, VI.B; Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -360-362; Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -028-030; FDA Response (LIQ\_PH-ILD\_00120424) at -424-427; Weidman Email re: Pre-sNDA Meeting (LIQ\_PH-ILD\_00148509) at -509; Rajeev Saggar Dep. Tr. at 67:20-68:13, 68:14-69:4, 70:11-72:16; 77:3-79:9; 84:24-85:1, 96:17-97:1, 195:20-197:23, 212:5-213:1; *see generally* INCREASE publication (UTC\_PH-ILD\_010790).

<sup>580</sup> Channick Reb. Rpt. ¶ 62.

<sup>581</sup> See *supra* § III.C; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-021, -031-033; FDA’s Labeling Resources for Human Prescription Drugs | FDA.pdf (7-Feb-2025) (UTC\_PH-ILD\_227394) (“Human prescription drug labeling ... [c]ontains a summary of the essential scientific information needed for the safe and effective use of the drug[.]” (emphasis added)); U.S. Food & Drug Admin., Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (2006) (UTC\_PH-ILD\_227354) at -359 (“The primary objective of the CLINICAL STUDIES section is to summarize (1) the evidence supporting effectiveness in the subjects who were studied, (2) the critical design aspects of the studies, including the populations studied and endpoints measured, and (3) the important limitations of the available evidence.” (emphasis added)).

the peer-reviewed literature as demonstrating the safety and efficacy of Yutrepia in PH-ILD.<sup>582</sup> Nonetheless, as discussed above, infringement only requires employing a method that provides the recited treatment effects, and that method is express in the tentatively approved Yutrepia label.<sup>583</sup>

235. Nonetheless, Dr. Channick mischaracterizes Dr. Nathan's positions as describing "administration of Yutrepia™[] without more."<sup>584</sup> For all claims, the INCREASE study identified that inhaled treprostinil yielded treatment effects with a reasonable degree of statistical certainty in PH-ILD patients, and those findings attached to Yutrepia.<sup>585</sup> It is Dr. Channick who is improperly overlooking key information available to the POSA and that is also embedded and explicitly referenced in the Yutrepia label—the INCREASE study. Accordingly, I disagree with Dr. Channick's personal opinion "that direct infringement of these claims requires a healthcare provider or patient to *actively measure* whether Yutrepia™ administration produces the claimed statistically significant outcomes."<sup>586</sup> But the claims do not require this, and regardless it is unnecessary with respect to Yutrepia in view of the INCREASE study and especially in view of

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<sup>582</sup> See *supra* §§ III.C, IV.A, VI.B; Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -360-362; Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -028-030; FDA Response (LIQ\_PH-ILD\_00120424) at -424-427; Weidman Email re: Pre-sNDA Meeting (LIQ\_PH-ILD\_00148509) at -509; Rajeev Saggar Dep. Tr. at 67:20-68:13, 68:14-69:4, 70:11-72:16; 77:3-79:9; 84:24-85:1, 96:17-97:1, 195:20-197:23, 212:5-213:1.

<sup>583</sup> See *supra* §§ IV.A, VI.B; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -026-027, -031-033).

<sup>584</sup> Channick Reb. Rpt. ¶ 62.

<sup>585</sup> *Supra* §§ III.B, III.C, IV.A VI.B; Thisted Reb. Rpt. §§ VII, IX-XI, XV; see generally INCREASE publication (UTC\_PH-ILD\_010790); see generally INCREASE Protocol (UTC\_PH-ILD\_145360); see generally Nathan 2021 (UTC\_PH-ILD\_147114); Original NDA 213005 § 2.2 (LIQ\_PH-ILD\_00046359) at -360-362; Original NDA 213005 § 2.5 (LIQ\_PH-ILD\_00045509) at -515-518; Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -028-030; FDA Response (LIQ\_PH-ILD\_00120424) at -424-427; Weidman Email re: Pre-sNDA Meeting (LIQ\_PH-ILD\_00148509) at -509; Rajeev Saggar Dep. Tr. at 67:20-68:13, 68:14-69:4, 70:11-72:16; 77:3-79:9; 84:24-85:1, 96:17-97:1, 195:20-197:23, 212:5-213:1.

<sup>586</sup> Channick Reb. Rpt. ¶ 62 (emphasis in original).

the tentatively approved Yutrepia label.<sup>587</sup> This is also why Dr. Channick's position regarding what the "POSA would understand" is wrong.<sup>588</sup> The POSA would at least have Yutrepia's label and the INCREASE study information and data cited therein,<sup>589</sup> and thus not need to "prescribe inhaled treprostinil (apply the intervention)[] to multiple patients (a group large enough to detect a meaningful difference), measure one of the selected parameters in each group member, aggregate the results from the patients, and then perform statistical analysis on those results."<sup>590</sup> Instead, the treatment course need only be undertaken in accordance with Yutrepia's label.<sup>591</sup>

236. Dr. Channick also asserts that the direct infringer's knowledge or understanding of their infringement is relevant to infringing the limitations of dependent claims 2, 4, and 6-10.<sup>592</sup> Dr. Channick appears to take the position that this knowledge or understanding is an independent rationale for direct infringement requiring evidence of infringing healthcare providers "conducting a statistical analysis of the patients they treat" and infringing "healthcare providers or patients

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<sup>587</sup> See *supra* §§ III.B, III.C, IV.A VI.B; Thisted Reb. Rpt. §§ VII, IX-XI, XV; see generally INCREASE publication (UTC\_PH-ILD\_010790); see generally INCREASE Protocol (UTC\_PH-ILD\_145360); see generally Nathan 2021 (UTC\_PH-ILD\_147114); compare Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -031-033 with INCREASE Protocol (UTC\_PH-ILD\_145360) at -470-471.

<sup>588</sup> Channick Reb. Rpt. ¶¶ 61, 92.

<sup>589</sup> See *supra* § III.D.2, IV.A, IV.B; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -026-027, -031-033; Pre-sNDA Meeting Request (LIQ\_PH-ILD\_00134026) at -028-030; FDA Response (LIQ\_PH-ILD\_00120424) at -424-427.

<sup>590</sup> See *supra* §§ III.D.2, IV.A, VI.B; see Channick Reb. Rpt. ¶¶ 61, 92.

<sup>591</sup> See *supra* §§ III.D.2, IV.A, VI.B; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020-022, -026-027, -031-033.

<sup>592</sup> Channick Reb. Rpt. at ¶ 61 ("Thus, a healthcare provider will not know or understand if they directly infringe any of claims 2, 4, 6, 7-8 and 9-10 without conducting a statistical analysis of the patients they treat."); *id.* at ¶ 62 ("Because Dr. Nathan's report is devoid of any evidence showing that healthcare providers or patients perform these calculations when administering Yutrepia™, or that they would have knowledge or understanding that these outcomes will be met, I am of the opinion that this alone is enough to defeat any allegations that Liquidia directly infringes claims 2, 4, 6, and 7-10.")

perform . . . calculations when administering Yutrepia™.”<sup>593</sup> I understand from counsel that whether a direct infringer knows or understands they are infringing the limitations added by these dependent claims is not relevant. Also, as discussed in this section, Dr. Channick’s position overlooks the knowledge and understanding that the INCREASE study provides to the POSA, including the INCREASE study data that is recited in the tentatively approved Yutrepia label.

237. In view of the foregoing, I also disagree with Dr. Channick’s position that proving inducement requires evidencing that:

Liquidia instructs or encourages healthcare providers and/or patients to treat a sufficiently large number of patients, measure the metric of interest, aggregate the collected data, and perform statistical analysis on the data. Indeed, Dr. Nathan does not point to any evidence, in the Yutrepia™ label, Liquidia’s marketing materials, or any other document, showing that Liquidia will instruct or encourage healthcare providers and/or patients to treat a sufficiently large number of patients, measure the metric of interest, aggregate the collected data, and perform statistical analysis on the data.<sup>594</sup>

As detailed above, Asserted Claims 2, 4, and 6-10 do not require healthcare providers and/or patients to do any of these acts expressly or implicitly. Instead, Asserted Claims 2, 4, and 6-10 distinguish methods of administering inhaled treprostinil to PH-ILD patients that achieve (i.e., provide) the respective treatment effect at the population level. Moreover, the INCREASE study has already established that administering inhaled treprostinil to PH-ILD patients provides statistically significant treatment effects with respect to 6MWD, plasma NT-proBNP concentration, risk of exacerbations due to interstitial lung disease, risk of clinical worsening events due to interstitial lung disease, and forced vital capacity.<sup>595</sup> Therefore, Yutrepia’s tentatively approved label does not need to do anything more than instruct administering Yutrepia

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<sup>593</sup> Channick Reb. Rpt. at ¶¶ 61, 62.

<sup>594</sup> Channick Reb. Rpt. ¶ 93.

<sup>595</sup> *Supra* § III.D.2.

in PH-ILD patients consistent with the INCREASE study's dosing regimen to instruct, encourage, recommend and promote the use of the methods that claims 2, 4, and 6-10 respectively distinguish, and I disagree with Dr. Channick's assertion that the tentatively approved Yutrepia label requires instruction to do more.<sup>596</sup> Rather, the tentatively approved Yutrepia label by summarizing the INCREASE Study, instructs the use of methods of claims 2, 4, and 6-10.

## **VII. DR. CHANNICK IS WRONG REGARDING INFRINGEMENT OF THE ASSERTED CLAIMS**

238. Contrary to Dr. Channick's opinions, the administration of Liquidia's proposed Yutrepia product to patients having PH-ILD as instructed by Liquidia's proposed labeling and package insert will infringe each of the Asserted Claims of the '327 patent. This opinion is based on the rationale described above. I provide specific evidence below to support that said administration of Yutrepia will directly infringe each of the Asserted Claims despite Dr. Channick's opinions to the contrary.

239. Further, it is my opinion that Liquidia will induce patients, caregivers, and clinicians to infringe each of the Asserted Claims by instructing administration of Yutrepia according to the instructions set forth in the proposed labeling and package insert as described both above and below. My opinion that Liquidia will induce and contribute to infringement of the Asserted Claims is further supported by Liquidia's own proposed marketing materials, which seek to promote Yutrepia for PH-ILD consistent with infringement of the Asserted Claims.<sup>597</sup>

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<sup>596</sup> Channick Reb. Rpt. ¶¶ 94-95.

<sup>597</sup> See, e.g., '327 patent (UTC\_PH-ILD\_005310); Yutrepia Draft Webpage 2 (LIQ\_PH-ILD\_00146936) at -937 ("In a clinical study, patients with PH-ILD who took an inhaled treprostinil solution walked further on average and lowered the chance of their PH-ILD worsening than those who took a placebo solution."); Yutrepia Marketing Diagram (LIQ\_PH-ILD\_00147156) at -157 (describing the improvement in 6MWD and reduction in the risk of a clinical worsening event observed in INCREASE trial patients); Yutrepia Formulary Kit (LIQ\_PH-ILD\_00146970) at -977 (describing the 6MWD, NT-proBNP, and reduction in clinical

**A. Liquidia's Yutrepia Will Infringe Claim 1.**

**1. "A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising"**

240. It is my opinion that administering Yutrepia according to Liquidia's proposed labeling will infringe this limitation of claim 1 of the '327 patent. This is clear because the Yutrepia proposed labeling and the INCREASE study on which the proposed labeling relies report improving exercise capacity as claimed. Accordingly, it is more likely than not that patients administered Yutrepia will experience the beneficial effect of an improvement in exercise capacity as claimed.

241. As described above, "Yutrepia is indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability."<sup>598</sup>

242. Furthermore, the Yutrepia label and the INCREASE data (which is relied upon in the Yutrepia label) report improvements in 6MWD which a POSA would understand as an improvement in exercise capacity as claimed.<sup>599</sup>

**2. "administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease,"**

243. It is my opinion that administering Yutrepia according to Liquidia's proposed labeling will directly infringe this limitation of claim 1 of the '327 patent. This is clear because

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worsening data from INCREASE); Yutrepia Marketing Handout (LIQ\_PH-ILD\_00147141) at -147-148 (describing the statistically significant improvement in 6MWD and the 39% risk reduction of a clinical worsening event); Yutrepia Presentation (LIQ\_PH-ILD\_00147196) at -236 (showcasing the statistically significant improvement in 6MWD and the reduction in risk of clinical worsening observed in the INCREASE trial).

<sup>598</sup> *Supra* § IV.A.1; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021.

<sup>599</sup> *Infra* § VII.B.-VII.C,

the Yutrepia proposed labeling instructs treating PH-ILD patients with the inhaled treprostinil as claimed.

244. The dosage form of Yutrepia is “inhalation powder contained in capsule” and the label instructs that the capsules are “[f]or oral inhalation only.”<sup>600</sup>

**3. “an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof”**

245. It is my opinion that administering Yutrepia according to Liquidia’s proposed labeling will infringe this limitation of claim 1 of the ’327 patent. This is clear because the Yutrepia proposed labeling instructs dosing at least 15 micrograms of treprostinil during a single treatment session.

246. As explained above, “Yutrepia contains treprostinil sodium” as the active ingredient.<sup>601</sup> More specifically, “[e]ach 5 mg of YUTREPIA inhalation powder contains 26.5 mcg of treprostinil, where 26.5 mcg of treprostinil is equivalent to 28 mcg of treprostinil sodium.”<sup>602</sup> *In vitro* testing further specifies that when using the lowest available capsule strength of 26.5 mcg, the amount of treprostinil delivered to the patient administered Yutrepia will be 15.1 mcg.<sup>603</sup> The Yutrepia label also instructs a starting dose of “26.5 mcg 3 to 5 times per day” and a target maintenance dosage of “79.5-106 mcg, 4 times daily.”<sup>604</sup>

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<sup>600</sup> *Supra* § IV.A.1; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -020.

<sup>601</sup> *Supra* § IV.A.1; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -026.

<sup>602</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -026.

<sup>603</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -027.

<sup>604</sup> *Supra* § IV.A.1; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022.

**4. “in a single administration event that comprises at least 6 micrograms per breath.”**

247. It is my opinion that administering Yutrepia according to Liquidia’s proposed labeling will infringe this limitation of claim 1 of the ’327 patent. This is clear from the dosing instructed in the Yutrepia proposed label.

248. As explained above, each capsule of Yutrepia is delivered in 2 breaths, regardless of strength, with the lowest strength being 26.5 mcg.<sup>605</sup> *In vitro* testing by Liquidia also confirmed that the 26.5 mcg capsule strength corresponds with a 15.1 mcg dose of treprostinil delivered to the patient.<sup>606</sup> When a patient consumes that capsule strength in two breathes as instructed, that amounts to 7.55 mcg per breath.

**B. Liquidia’s Yutrepia Will Infringe Claim 2.**

**1. “The method of claim 1, wherein said administering provides a statistically significant increase of a 6 minutes walk distance in the patient after 8 weeks, 12 weeks, or 16 weeks.”**

249. Claim 2 depends from claim 1. As described above, administering Yutrepia according to Yutrepia’s tentatively approved labeling will meet all of the limitations of claim 1. Claim 2 additionally requires that the “administering provides a statistically significant increase of a 6 minutes walk distance in the patient after 8 weeks, 12 weeks, or 16 weeks.” I also understand that because the timepoint limitations are listed in the alternative (“8 weeks, 12 weeks, *or* 16 weeks”) that means acts satisfying any one of those timepoints is sufficient to infringe claim 2, i.e., infringing acts do not require satisfying all three time points.

250. Dr. Channick asserts:

The Hodges-Lehmann estimate that [Yutrepia’s tentatively approved label recites] only describes a statistically significant improvement in 6MWD shown in a prior clinical study (the

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<sup>605</sup> *Supra* § IV.A.1; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022.

<sup>606</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -027.

INCREASE study, which was completed in 2021), using a different drug formulation (Tyvaso® (i.e., treprostinil inhalation solution)—not Yutrepia™ (i.e., treprostinil inhalation dry powder)). The same is true of the Forest Plot [Yutrepia’s tentatively approved label recites] which . . . ‘compares patients taking Tyvaso (treprostinil) with patients administered placebo’ and shows statistically significant improvement in 6MWD. In my opinion, a POSA reading the Hodges-Lehmann estimate and Forest Plot would only understand that a statistically significant improvement in 6MWD resulted from administration of treprostinil inhalation solution in the group of patients treated in the INCREASE study.<sup>607</sup>

I disagree with Dr. Channick that a direct infringer would need to “*understand*” whether they are infringing in the way that Dr. Channick suggests is necessary. I also disagree with Dr. Channick asserting that the INCREASE study’s 6MWD outcomes do not inform Yutrepia outcomes.<sup>608</sup> That is wrong for at least two reasons that I detailed above.<sup>609</sup> First, the Yutrepia sNDA for the PH-ILD indication relies entirely on the INCREASE study for evidence of clinical efficacy in PH-ILD patients, which is consistent with the tentatively approved Yutrepia label that only recites clinical support for the listed PH-ILD indication as the INCREASE study.<sup>610</sup> Therefore, as I have been informed by counsel, Yutrepia is bound by its label with respect to the PH-ILD indication, and for the purpose of considering infringement in this case, Yutrepia is administered according to its label—i.e., consistent with the INCREASE study—and thus necessarily performs according to the INCREASE study.<sup>611</sup> That includes the statistically significant treatment effects with respect to 6MWD at 8, 12, and 16 weeks after initiation of inhaled treprostinil, which as discussed above are at least evidenced by the Hodges-Lehmann estimate and forest plot analyses that are expressly

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<sup>607</sup> Channick Reb. Rpt. ¶ 65.

<sup>608</sup> Channick Reb. Rpt. ¶ 65; *see also id.* ¶ 102 (“While the Yutrepia™ label does discuss improvements in six-minute walk distance, it only does so in the context of clinical trials with Tyvaso® (the TRIUMPH and INCREASE trials”).

<sup>609</sup> *Supra* §§ VI.B-C.

<sup>610</sup> *Supra* § VI.B.

<sup>611</sup> *Supra* § VI.B.

recited on Yutrepia's tentatively approved label.<sup>612</sup> I note the foregoing applies equally to Asserted Claims 3 and 17-19 that I address below.<sup>613</sup>

251. Second, as far as I am aware, there is no scientific basis for Dr. Channick's attempts to disassociate Yutrepia from the INCREASE study's outcomes.<sup>614</sup> And further, Dr. Channick's opinions in this regard are directly contrary to Liquidia's representations, including those made to FDA to obtain the PH-ILD indication for its Yutrepia product.<sup>615</sup> As explained above, because treprostinil is Yutrepia's only active ingredient and because Liquidia relies on INCREASE to support approval of its own product, the INCREASE study is sufficient evidence that administering Yutrepia to patients with PH-ILD will more likely than not exhibit the treatment effects that the INCREASE study reported.<sup>616</sup> Liquidia has also asserted that Yutrepia is biocomparable (satisfying the criteria for bioequivalence) with Tyvaso through its LTI-102 study, and Yutrepia's label instructs administering Yutrepia consistent with the INCREASE study, even going so far as to define the dosing between Tyvaso and Yutrepia as "equivalent" in the context of the INCREASE study.<sup>617</sup> Accordingly, in view of the INCREASE study, LTI-102, and Yutrepia's tentatively approved label, I have not seen persuasive evidence or reasoning from Dr. Channick to believe that Yutrepia will not meet or exceed the INCREASE study 6MWD outcomes.<sup>618</sup> In fact, that is what Liquidia's CMO has admitted and the position Liquidia takes

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<sup>612</sup> *Supra* §§ III.D.2, VI.B.

<sup>613</sup> *Infra* § VII.C.

<sup>614</sup> *Supra* § VI.B.

<sup>615</sup> *Supra* § VI.B.

<sup>616</sup> *Supra* §§ III.D.2, IV.A, VI.B.

<sup>617</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at -031; *supra* § IV.A.2.b.

<sup>618</sup> *Supra* §§ III.D.2, IV.A, VI.B.

publicly and in its proposed marketing materials.<sup>619</sup> I note the foregoing applies equally to Asserted Claims 3 and 17-19 that I address below.<sup>620</sup>

252. Also, as detailed above, claim 2 distinguishes methods of administering inhaled treprostinil to PH-ILD patients that achieve (i.e., provide) a 6MWD treatment effect at the population level at the respectively recited timepoints.<sup>621</sup> The tentatively approved Yutrepia label instructs administering Yutrepia according to the INCREASE study's dosing regimen, which as detailed above achieved a statistically significant 6MWD treatment effect at 8, 12, and 16 weeks.<sup>622</sup> Therefore, the demonstrated statistical significance of these 6MWD treatment effects in the INCREASE study leads me to conclude that administration of Yutrepia to PH-ILD patients consistent with Yutrepia's tentatively approved label will result in individual PH-ILD patients more likely than not exhibiting the 8-week, 12-week, or 16-week treatment effects identified in claim 2.<sup>623</sup> As detailed above, I disagree with Dr. Channick that infringing claim 2 requires:

[A] healthcare provider or patient to administer inhaled treprostinil over a period of at least 8 weeks, measure the 6MWD prior to administering the drug and after a period of at least 8 weeks, after 12 weeks, or after 16 weeks and, for claims 2 and 8, assess whether there is any statistically significant improvement in 6MWD.<sup>624</sup>

Moreover, Dr. Channick misunderstands claim 2 in this regard, asserting:

In my opinion, a POSA reading the Hodges-Lehmann estimate and Forest Plot would only understand that a statistically significant improvement in 6MWD resulted from administration of treprostinil inhalation solution in the group of patients treated in the INCREASE study.<sup>625</sup>

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<sup>619</sup> *Supra* §§ IV.B, VI.B.

<sup>620</sup> *Infra* § VII.C.

<sup>621</sup> *Supra* § VI.C.

<sup>622</sup> *Supra* §§ III.D.2, IV.A, VI.C.

<sup>623</sup> *Supra* §§ III.D.2, IV.A, VI.C.

<sup>624</sup> *Supra* § VI.C; Channick Reb. Rpt. ¶ 64.

<sup>625</sup> Channick Reb. Rpt. ¶ 65.

What is critical with respect to claim 2 is that the INCREASE study identified methods of administering inhaled treprostinil that achieved statistically significant treatment effects, which are the methods that claim 2 is directed to, and Yutrepia's tentatively approved label instructs performing these methods.<sup>626</sup> Accordingly, I disagree with Dr. Channick's position that infringement of claim 2 requires any instruction, implicit or express, "to measure 6MWD after weeks 8, 12 or 16, let alone treat multiple patients, measure 6MWD, aggregate the data, and perform a statistical analysis" or proving in any way that those acts would occur.<sup>627</sup> That is at least because, as detailed above, those acts are not required by claim 2 in view of the INCREASE study's outcomes, and the tentatively approved Yutrepia label instructs administering Yutrepia consistent with the INCREASE study's dosing regimen. I note the foregoing applies equally as relevant to Asserted Claim 8.<sup>628</sup>

253. Therefore, it is my opinion that administering Yutrepia according to Yutrepia's tentatively approved labeling will infringe claim 2 of the '327 patent. This is clear because Yutrepia's tentatively approved labeling and the INCREASE study on which it relies report methods of administering inhaled treprostinil to PH-ILD patients that achieve statistically significant treatments effects with respect to 6MWD, specifically improvement in 6MWD after 8 weeks, 12 weeks, or 16 weeks as claimed.<sup>629</sup> Accordingly, it is more likely than not that patients administered Yutrepia consistent with its tentatively approved label will experience an inhaled treprostinil treatment effect with respect to 6MWD after 8 weeks, 12 weeks, or 16 weeks that was reported by the INCREASE study.<sup>630</sup>

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<sup>626</sup> *Supra* §§ III.D.2, IV.A.

<sup>627</sup> Channick Reb. Rpt. ¶¶ 65-66.

<sup>628</sup> *Infra* § VII.H.

<sup>629</sup> *Supra* §§ III.D.2, IV.A.

<sup>630</sup> *Supra* §§ III.D.2, IV.A.

254. Dr. Channick asserts that “a POSA reading the Hodges-Lehmann estimate and Forest Plot would only understand that a statistically significant improvement in 6MWD resulted from administration of treprostinil inhalation solution in the group of patients treated in the INCREASE study.”<sup>631</sup> I disagree that a POSA’s reading would be so limited. Rather, a POSA would apply the findings from the INCREASE data relating to 6MWD to PH-ILD patients administered Yutrepia consistent with Yutrepia’s tentatively approved label.<sup>632</sup>

255. As explained above, the INCREASE study reported statistically significant treatment effects with respect to 6MWD, specifically improvements in 6MWD after 8 weeks, 12 weeks, and 16 weeks, using at least three statistical methods: MMRM, MCMC, and Hodges-Lehmann Estimate.<sup>633</sup> The MMRM analysis reported a p-value of  $P < 0.001$  at week 8, week 12, and week 16.<sup>634</sup> The MCMC analysis reported a p-value of  $P < 0.001$  at week 16.<sup>635</sup> The Hodges-Lehmann Estimate reported a p-value of  $P = 0.0104$  at week 8 and  $P = 0.004$  at week 12 and week 16.<sup>636</sup>

256. Furthermore, the tentatively approved Yutrepia label expressly reports the INCREASE study’s 6MWD outcomes, detailing that administering inhaled treprostinil to PH-ILD patients provided statistically significant treatment effects with respect to 6MWD, specifically improvements in 6MWD after 8 weeks, 12 weeks, and 16 weeks. To evidence this, the tentatively approved Yutrepia label reports that a Hodges-Lehmann estimate yielded a p-value of  $P = 0.004$  at

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<sup>631</sup> Channick Reb. Rpt. ¶ 65.

<sup>632</sup> *Supra* §§ III.D.2, IV.A.

<sup>633</sup> *Supra* § III.D.2.

<sup>634</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -813; INCREASE CSR (UTC\_PH-ILD\_055371) at -444.

<sup>635</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -793.

<sup>636</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -818; INCREASE CSR (UTC\_PH-ILD\_055371) at -376.

week 16 and provides the 95% confidence intervals for the Hodges-Lehmann estimates at 8, 12, and 16 weeks.<sup>637</sup> None of the 95% confidence intervals cross zero, which a POSA would understand as indicating statistical significance was achieved.<sup>638</sup>

257. Dr. Channick attempts to support his non-infringement position by asserting that “[t]here is nothing in the Yutrepia™ label that instructs the measurement of 6MWD and in fact, 6MWD is not, in my experience, routinely conducted in clinical practice in the context of treating PH-ILD patients outside of clinical studies.”<sup>639</sup> However, claim 2 does not require that 6MWD be measured at all. Claim 2 is directed to methods of administering treprostinil that provide a statistically significant treatment effect with respect to 6MWD. Measuring the change in 6MWD would not affect whether a patient experienced such a treatment effect, it would merely document it. Under Dr. Channick’s interpretation, a 6MWD treatment effect would not occur unless it was measured. I disagree. That is because, as detailed above, administering Yutrepia according to its tentatively approved label would more likely than not result in that patient experiencing the 6MWD treatment effects reported by the INCREASE study, and thus would more likely than not infringe the claim.

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<sup>637</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at-031.

<sup>638</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at-032.

<sup>639</sup> Channick Reb. Rpt. ¶ 65.

**C. Liquidia's Yutrepia Will Infringe Claims 3 and 17 through 19**

**1. Claim 3: “The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks.”**

**Claim 17: “The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks.”**

**Claim 18: “The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 12 weeks.”**

**Claim 19: “The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 16 weeks.”**

258. Claims 3 and 17-19 depend from claim 1. As described above, administering Yutrepia according to Liquidia's proposed labeling will meet all of the limitations of claim 1. Claim 3 additionally requires that the “administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks.” I also understand that because the timepoint limitations are listed in the alternative (“8 weeks, 12 weeks, *or* 16 weeks”) that means acts satisfying any one of those timepoints is sufficient to infringe claim 3, i.e., infringing acts do not require satisfying all three time points.

259. Claims 17-19 additionally require that the “administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks”; that the “administering increases a 6 minutes walk distance of the patient by at least 15 m after 12 weeks”; and that the “administering increases a 6 minutes walk distance of the patient by at least 15 m after 16 weeks,” respectively.

260. Therefore, it is my opinion that administering Yutrepia according to Yutrepia's tentatively approved label will infringe claims 3 and 17-19 of the '327 patent because the INCREASE study on which Yutrepia's tentatively approved labeling relies reported methods of administering inhaled treprostinil to PH-ILD patients that yield increases in 6MWD of at least 10m

and 15m after at least 8 weeks, 12 weeks, and 16 weeks as respectively claimed.<sup>640</sup> Accordingly, it is more likely than not that PH-ILD patients administered Yutrepia consistent with its tentatively approved label will more likely than not experience the beneficial effect of an increase in 6MWD of at least 10m or 15m after at least 8 weeks, 12 weeks, or 16 weeks that was reported by the INCREASE study.<sup>641</sup>

261. Dr. Channick asserts that “a POSA reading the Hodges-Lehmann estimate and Forest Plot would only understand that a statistically significant improvement in 6MWD resulted from administration of treprostinil inhalation solution in the group of patients treated in the INCREASE study.”<sup>642</sup> I disagree that a POSA’s reading would be so limited. Rather, a POSA would apply the findings from the INCREASE data relating to 6MWD to PH-ILD patients administered Yutrepia consistent with Yutrepia’s tentatively approved label.<sup>643</sup>

262. As explained above, the INCREASE study reported an increase in 6MWD by at least 15 m after 8 weeks, 12 weeks, and 16 weeks using at least three statistical methods: MMRM, MCMC, and Hodges-Lehmann estimate.<sup>644</sup> The MMRM analysis reported an increase in 6MWD of 24.13 m after 8 weeks, 31.29 m after 12 weeks and 31.12 after 16 weeks.<sup>645</sup> The MCMC analysis reported an increase in 6MWD of 22.84 m after 8 weeks, 29.2 m after 12 weeks, and 30.97 m after 16 weeks.<sup>646</sup> The Hodges-Lehmann estimate reported an increase in 6MWD of 15 m after 8 weeks, 20 m after 12 weeks, and 21 m after 16 weeks.<sup>647</sup>

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<sup>640</sup> *Supra* §§ III.D.2, IV.A.

<sup>641</sup> *Supra* §§ III.D.2, IV.A.

<sup>642</sup> Channick Reb. Rpt. ¶ 65.

<sup>643</sup> *Supra* § VII.B.

<sup>644</sup> *Supra* § III.D.2.

<sup>645</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -813.

<sup>646</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -815.

<sup>647</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -818.

263. Furthermore, the tentatively approved Yutrepia label reports the INCREASE study's 6MWD outcomes, detailing that administering inhaled treprostinil to PH-ILD patients provided improvements in 6MWD by at least 15 m after 8 weeks, 12 weeks, and 16 weeks using the Hodges-Lehmann estimate.<sup>648</sup> The Hodges-Lehmann estimate reported an improvement in 6MWD of 15 m after 8 weeks, 20 m after 12 weeks, and 21 m after 16 weeks.<sup>649</sup>

264. Dr. Channick attempts to support his non-infringement position by asserting that “[t]here is nothing in the Yutrepia™ label that instructs the measurement of 6MWD and in fact, 6MWD is not, in my experience, routinely conducted in clinical practice in the context of treating PH-ILD patients outside of clinical studies.”<sup>650</sup> However, claims 3 and 17 through 19 do not require that 6MWD be measured at all. Instead claims 3 and 17 through 19 are directed to methods of administering treprostinil that yield a beneficial effect. Measuring the change in 6MWD would not affect whether a PH-ILD patient experienced such a beneficial effect, it would merely document it. Under Dr. Channick's interpretation, an improvement in 6MWD would not occur unless it was measured. I disagree. That is because, as detailed above, administering Yutrepia according to its label would infringe the claims 3 and 17-19.

**D. Liquidia's Yutrepia Will Infringe Claim 4**

**1. “The method of claim 1, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks.”**

265. Claim 4 depends from claim 1. As described above, administering Yutrepia according to Liquidia's proposed labeling will meet all of the limitations of claim 1. Claim 4 additionally requires that the “administering provides a statistically significant reduction of a

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<sup>648</sup> *Supra* § IV.A.3.a.

<sup>649</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at-032.

<sup>650</sup> Channick Reb. Rpt. ¶ 65.

plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks.” I also understand that because the timepoint limitations are listed in the alternative (“8 weeks, 12 weeks, or 16 weeks”) that means satisfaction of the claimed “reduction” at any one of those timepoints is sufficient to infringe claim 4, i.e., infringing does not require satisfying all three time points.

266. Dr. Channick asserts:

I still do not believe [the INCREASE] publication is proof of future direct infringement by healthcare providers because it merely describes past data of a different drug, which does not instruct healthcare providers and/or patients to practice the steps outlined in claims 4 and 5.<sup>651</sup>

And Dr. Channick similarly asserts:

[The INCREASE] publication describes the effects of Tyvaso® administration on NT-proBNP levels. A POSA reading this publication would not make the leap that Yutrepia™ administration would result in the same NT-proBNP levels.<sup>652</sup>

I disagree with Dr. Channick asserting that the INCREASE study’s NT-proBNP plasma concentration outcomes do not inform Yutrepia outcomes. That is wrong for at least two reasons that I detailed above.<sup>653</sup> First, the Yutrepia sNDA for the PH-ILD indication relies entirely on the INCREASE study for evidence of clinical efficacy in PH-ILD patients, which is consistent with the tentatively approved Yutrepia label that only recites clinical support for the listed PH-ILD indication is the INCREASE study.<sup>654</sup> Therefore, as I have been informed by counsel, Yutrepia is bound by its label with respect to the PH-ILD indication, and for the purpose of considering infringement in this case Yutrepia necessarily is administered according to its label—i.e., consistent with the INCREASE study—and thus necessarily performs according to the

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<sup>651</sup> Channick Reb. Rpt. ¶ 71.

<sup>652</sup> Channick Reb. Rpt. ¶ 72.

<sup>653</sup> *Supra* §§ VI.B-C.

<sup>654</sup> *Supra* § VI.B.

INCREASE study.<sup>655</sup> That at least includes the statistically significant treatment effects with respect to NT-proBNP plasma concentrations at 8 and 16 weeks after initiation of inhaled treprostinil, which as discussed above and herein are at least evidenced by the least-squares mean differences analyses that were reported by the INCREASE publication.<sup>656</sup> Although these data do not appear to be recited on Yutrepia's tentatively approved label, that label still instructs administering Yutrepia consistent with methods that the INCREASE Study demonstrated provided the statistically significant treatment effects in PH-ILD patients.<sup>657</sup> I note the foregoing applies equally to Asserted Claim 5 that I address below.<sup>658</sup>

267. Second, as far as I am aware there is no scientific basis for Dr. Channick's attempts to disassociate Yutrepia from the INCREASE study's outcomes.<sup>659</sup> And further, Dr. Channick's opinions in this regard are directly contrary to Liquidia's representations, including those made to FDA to obtain the PH-ILD indication for its Yutrepia product.<sup>660</sup> As explained above, because treprostinil is Yutrepia's only active ingredient and because Liquidia relies on INCREASE to support approval of its own product, the INCREASE study is sufficient evidence that administering Yutrepia to patients with PH-ILD will more likely than not exhibit the treatment effects that the INCREASE study reported.<sup>661</sup> Liquidia has also asserted that Yutrepia is biocomparable (satisfying the criteria for bioequivalence) with Tyvaso through its LTI-102 study, and Yutrepia's label instructs administering Yutrepia consistent with the INCREASE study.<sup>662</sup>

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<sup>655</sup> *Supra* § VI.B.

<sup>656</sup> *Supra* §§ III.D.2, VI.B.

<sup>657</sup> *Supra* §§ III.D.2, IV.A, VI.B.

<sup>658</sup> *Infra* § VII.E.

<sup>659</sup> *Supra* § VI.B.

<sup>660</sup> *Supra* § VI.B.

<sup>661</sup> *Supra* §§ III.D.2, IV.A, VI.B.

<sup>662</sup> *Supra* §§ IV.A, VI.B.

Accordingly, in view of the INCREASE study, LTI-102, and Yutrepia's tentatively approved label, I have not seen persuasive evidence or reasoning from Dr. Channick to believe that Yutrepia will not meet or exceed the INCREASE study NT-proBNP plasma concentration outcomes.<sup>663</sup> In fact, that is what Liquidia's CMO has admitted and the position Liquidia takes publicly and in its proposed marketing materials.<sup>664</sup> I note the foregoing applies equally to Asserted Claim 5 that I address below.<sup>665</sup>

268. Also, as detailed above, claim 4 distinguishes methods of administering inhaled treprostinil to PH-ILD patients that achieve (i.e., provide) a NT-proBNP plasma concentration treatment effect at the population level at the respectively recited timepoints.<sup>666</sup> The tentatively approved Yutrepia label instructs administering Yutrepia according to the INCREASE study's dosing regimen, which as detailed above achieved a statistically significant NT-proBNP plasma concentration treatment effect at 8 and 16 weeks.<sup>667</sup> Therefore, the demonstrated statistical significance of these NT-proBNP plasma concentration treatment effects in the INCREASE study leads me to conclude that administration of Yutrepia to PH-ILD patients consistent with Yutrepia's tentatively approved label will result in individual PH-ILD patients more likely than not exhibiting the 8-week or 16-week treatment effects identified in claim 4.<sup>668</sup> As detailed above, I disagree with Dr. Channick that his Rebuttal Report's discussion under § V.B.1 applies in any way to claim 4.<sup>669</sup> The INCREASE study identified methods of administering inhaled treprostinil that achieved

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<sup>663</sup> *Supra* §§ III.D.2, IV.A, VI.B.

<sup>664</sup> *Supra* §§ IV.B, VI.B.

<sup>665</sup> *Infra* § VII.E.

<sup>666</sup> *Supra* § VI.C.

<sup>667</sup> *Supra* §§ III.D.2, IV.A, VI.C.

<sup>668</sup> *Supra* §§ III.D.2, IV.A, VI.C.

<sup>669</sup> Channick Reb. Rpt. ¶ 106, § V.B.1.

statistically significant treatment effects, which are the methods that claim 4 is directed to, and Yutrepia's tentatively approved label instructs performing these methods.<sup>670</sup>

269. It is my opinion that administering Yutrepia according to Yutrepia's tentatively approved label will infringe claim 4 of the '327 patent because the INCREASE study on which Yutrepia's tentatively approved labeling relies reported methods of administering inhaled treprostinil to PH-ILD patients that achieve statistically significant treatments effects with respect to NT-proBNP plasma concentrations, specifically reductions in NT-proBNP plasma concentrations after at least 8 weeks and 16 weeks as claimed.<sup>671</sup> Accordingly, it is more likely than not that PH-ILD patients administered Yutrepia consistent with its tentatively approved label will experience an inhaled treprostinil treatment effect with respect to NT-proBNP plasma concentrations after 8 weeks or 16 weeks that was reported by the INCREASE study.<sup>672</sup>

270. Dr. Channick asserts that a "POSA reading [the INCREASE] publication would not make the leap that Yutrepia™ administration would result in the same NT-proBNP levels."<sup>673</sup> I disagree that a POSA's reading would be so limited. Rather, a POSA would apply the findings from the INCREASE study relating to NT-proBNP plasma concentrations to PH-ILD patients administered Yutrepia consistent with Yutrepia's tentatively approved label.<sup>674</sup>

271. As explained above, INCREASE reported statistically significant treatment effects with respect to NT-proBNP plasma concentrations, specifically reductions of NT-proBNP plasma concentrations after 8 weeks and 16 weeks using least-squares mean differences, expressed as a ratio, obtained from the analysis of covariance with change from baseline in log-transformed data

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<sup>670</sup> *Supra* § VI.C.

<sup>671</sup> *Supra* §§ III.D.2, IV.A.

<sup>672</sup> *Supra* §§ III.D.2, IV.A.

<sup>673</sup> Channick Reb. Rpt. ¶ 72.

<sup>674</sup> *Supra* §§ III.D.2, IV.A.

in NT-proBNP as the dependent variable, treatment as the fixed effect, and log-transformed baseline NT-proBNP as a covariate.<sup>675</sup> The resulting analysis reported a p-value of  $P < 0.001$  at week 8 and week 16.<sup>676</sup>

272. Furthermore, the Yutrepia Product Dossier advertises the same 16 week INCREASE study finding—a statistically significant reduction of NT-proBNP plasma concentration after 16 weeks.<sup>677</sup> The Yutrepia Product Dossier reported the same p-value of  $P < 0.001$  at week 16.<sup>678</sup>

273. Dr. Channick attempts to support his non-infringement position by asserting that “[t]he Yutrepia™ label never mentions NT-proBNP, let alone provides any instruction to measure this parameter” and that “outside of clinical trial settings, healthcare providers treating PH-ILD patients do not routinely measure NT-proBNP levels.”<sup>679</sup> However, claim 4 does not require that NT-proBNP levels be measured at all. Claim 4 is directed to methods of administering treprostinil that provide a statistically significant treatment effect with respect to NT-proBNP plasma concentrations. Measuring the change in NT-proBNP plasma concentrations would not affect whether a patient experienced such a treatment effect, it would merely document it. Under Dr. Channick’s interpretation, a reduction in NT-proBNP levels would not exist unless it was measured. I disagree. That is because, as detailed above, administering Yutrepia according to its tentatively approved label would infringe claim 4.

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<sup>675</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -816.; *supra* § III.D.2.

<sup>676</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -816; *supra* § III.D.2.

<sup>677</sup> Product Dossier (LIQ\_PH-ILD\_00146984) at -037-038; ; *supra* § III.D.2, IV.C.

<sup>678</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at-037-038.

<sup>679</sup> Channick Reb. Rpt. ¶ 70.

**E. Liquidia's Yutrepia Will Infringe Claim 5**

- 1. “The method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks.”**

274. Claim 5 depends from claim 1. As described above, administering Yutrepia according to Liquidia's proposed label will meet all of the limitations of the method of claim 1. Claim 5 additionally requires that the “administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks.” I also understand that because the timepoint limitations are listed in the alternative (“8 weeks, 12 weeks, or 16 weeks”) that means acts satisfying any one of those timepoints is sufficient to infringe claim 5, i.e., infringing acts do not require satisfying all three time points.

275. It is my opinion that administering Yutrepia according to Yutrepia's tentatively approved label will infringe claim 5 of the '327 patent because the INCREASE study on which Yutrepia's tentatively approved labeling relies reported methods of administering inhaled treprostinil to PH-ILD patients that yield a reduction of NT-proBNP plasma concentration by at least 200 pg/ml after at least 8 weeks and 16 weeks as claimed.<sup>680</sup> Accordingly, it is more likely than not that PH-ILD patients administered Yutrepia consistent with its tentatively approved label will more likely than not experience the beneficial effect of a reduction in NT-proBNP plasma concentration by at least 200 pg/ml after at least 8 weeks or 16 weeks that was reported by the INCREASE study.<sup>681</sup>

276. Dr. Channick asserts that a “POSA reading [the INCREASE] publication would not make the leap that Yutrepia™ administration would result in the same NT-proBNP levels.”<sup>682</sup>

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<sup>680</sup> *Supra* § III.D.2, IV.A.

<sup>681</sup> *Supra* § III.D.2, IV.A.

<sup>682</sup> Channick Reb. Rpt. ¶ 72.

I disagree that a POSA's reading would be so limited. Rather, a POSA would apply the findings from the INCREASE data relating to NT-proBNP plasma concentration to PH-ILD patients administered Yutrepia consistent with Yutrepia's tentatively approved label.<sup>683</sup>

277. As explained above, the INCREASE publication reported a reduction of NT-proBNP plasma concentration by at least 200 pg/ml after 16 weeks.<sup>684</sup> The mean reduction of NT-proBNP levels in the inhaled treprostinil treatment group was 396.35 pg/ml at week 16.<sup>685</sup> Meanwhile, the mean increase of NT-proBNP levels in the placebo group was 1453.95 pg/ml at week 16.<sup>686</sup> As such, the difference in mean change of NT-proBNP levels between the inhaled treprostinil group and placebo group was 1,850.3 pg/ml. A POSA would understand that both 396.35 pg/ml and 1,850.3 pg/ml are at least 200 pg/ml.

278. Furthermore, the Yutrepia Product Dossier references these results of the INCREASE study, reporting the same reduction of NT-proBNP levels by at least 200 pg/ml after 16 weeks.<sup>687</sup> The Yutrepia Product Dossier reported a mean reduction of NT-proBNP plasma concentration by 396.35 pg/mL at week 16 in inhaled treprostinil-treated PH-ILD patients and a mean increase of NT-proBNP plasma concentrations of 1453.95 pg/ml at week 16 in placebo-treated patients.<sup>688</sup>

279. As explained above, the INCREASE CSR reported a reduction of NT-proBNP plasma concentration by at least 200 pg/ml after 8 weeks.<sup>689</sup> The mean reduction of NT-proBNP

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<sup>683</sup> *Supra* § VII.D.

<sup>684</sup> *Supra* § III.D.2.b.2.

<sup>685</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -797.

<sup>686</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -797.

<sup>687</sup> Product Dossier (LIQ\_PH-ILD\_00146984) at -037.

<sup>688</sup> Product Dossier (LIQ\_PH-ILD\_00146984) at -037.

<sup>689</sup> *Supra* § III.D.2.b.2.

plasma concentration in the inhaled treprostinil treatment group was 480.81 pg/ml at week 8.<sup>690</sup> Meanwhile, the mean increase of NT-proBNP plasma concentration in the placebo group was 604.05 pg/ml at week 8.<sup>691</sup> As such, the difference in mean change of NT-proBNP plasma concentration between the inhaled treprostinil group and placebo group was 1,084.9 pg/ml. A POSA would understand that both 480.81 pg/ml and 1,084.9 pg/ml are at least 200 pg/ml.

280. Dr. Channick attempts to support his non-infringement position by asserting that “[t]he Yutrepia™ label never mentions NT-proBNP, let alone provides any instruction to measure this parameter” and that “outside of clinical trial settings, healthcare providers treating PH-ILD patients do not routinely measure NT-proBNP levels.”<sup>692</sup> However, claim 5 does not require that NT-proBNP plasma concentration be measured at all. Claim 5 is directed to methods of administering inhaled treprostinil that yield a reduction in NT-proBNP plasma concentration. Measuring the change in NT-proBNP plasma concentration would not affect whether a PH-ILD patient experienced such a beneficial effect, it would merely document it. Under Dr. Channick’s interpretation, a reduction in NT-proBNP plasma concentration would not occur unless it was measured. I disagree. That is because, as detailed above, administering Yutrepia according to its tentatively approved label would infringe claim 5.

**F. Liquidia’s Yutrepia Will Infringe Claim 6**

**1. “The method of claim 1, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.”**

281. Claim 6 depends from claim 1. As described above, administering Yutrepia according to Liquidia’s proposed labeling will meet all of the limitations of claim 1.<sup>693</sup> Claim 6

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<sup>690</sup> INCREASE CSR (UTC\_PH-ILD\_055371) at -437.

<sup>691</sup> INCREASE CSR (UTC\_PH-ILD\_055371) at -437.

<sup>692</sup> Channick Reb. Rpt. ¶ 70.

<sup>693</sup> *Supra* § VII.A.

additionally requires that the “administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.”

282. Dr. Channick asserts:

These documents describe how Tyvaso® administration statistically significantly reduced disease exacerbations. In my opinion, a POSA would not naturally conclude from this that Yutrepia™ (which has a different formulation than Tyvaso®) would necessarily result in the same reduction of disease exacerbations since it is a different drug.<sup>694</sup>

I disagree with Dr. Channick asserting that the INCREASE study’s exacerbations of interstitial lung disease outcomes do not inform Yutrepia outcomes. That is wrong for at least two reasons that I detailed above.<sup>695</sup> First, the Yutrepia sNDA for the PH-ILD indication relies entirely on the INCREASE study for evidence of clinical efficacy in PH-ILD patients, which is consistent with the tentatively approved Yutrepia label that only recites clinical support for the listed PH-ILD indication as the INCREASE study.<sup>696</sup> Therefore, as I have been informed by counsel, Yutrepia is bound by its label with respect to the PH-ILD indication, and for the purpose of considering infringement in this case Yutrepia is administered according to its label—i.e., consistent with the INCREASE study—and thus necessarily performs according to the INCREASE study.<sup>697</sup> That includes the statistically significant treatment effects with respect to reducing the risk of exacerbations associated with interstitial lung disease, which as discussed above and herein are at least evidenced by the Fisher’s exact test, the log-rank test from the Cox proportional hazards model, and the chi-square test analyses that were reported by the INCREASE publication.<sup>698</sup> Although these data do not appear to be recited on Yutrepia’s tentatively approved label, that label

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<sup>694</sup> Channick Reb. Rpt. ¶ 76.

<sup>695</sup> *Supra* §§ VI.B-C.

<sup>696</sup> *Supra* § VI.B.

<sup>697</sup> *Supra* § VI.B.

<sup>698</sup> *Supra* §§ III.D.2, VI.B.

still instructs administering Yutrepia consistent with methods that the INCREASE Study results demonstrated provided the statistically significant treatment effects in PH-ILD patients.<sup>699</sup>

283. Second, as far as I am aware there is no scientific basis for Dr. Channick's attempts to disassociate Yutrepia from the INCREASE study's outcomes.<sup>700</sup> And further, Dr. Channick's opinions in this regard are directly contrary to Liquidia's representations, including those made to FDA to obtain the PH-ILD indication for its Yutrepia product.<sup>701</sup> As explained above, because treprostinil is Yutrepia's only active ingredient and because Liquidia relies on INCREASE to support approval of its own product, the INCREASE study is sufficient evidence that administering Yutrepia to patients with PH-ILD will more likely than not exhibit the treatment effects that the INCREASE study reported.<sup>702</sup> Liquidia has also asserted that Yutrepia is biocomparable (satisfying the criteria for bioequivalence) with Tyvaso through its LTI-102 study, and Yutrepia's label instructs administering Yutrepia consistent with the INCREASE study.<sup>703</sup> Accordingly, in view of the INCREASE study, LTI-102, and Yutrepia's tentatively approved label, I have not seen persuasive evidence or reasoning from Dr. Channick to believe that Yutrepia will not meet or exceed the INCREASE study outcomes with respect to reducing risk of exacerbations due to interstitial lung disease.<sup>704</sup> In fact, that is what Liquidia's CMO has admitted.<sup>705</sup>

284. Also, as detailed above, claim 6 distinguishes methods of administering inhaled treprostinil to PH-ILD patients that achieve (i.e., provide) a treatment effect at the population level

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<sup>699</sup> *Supra* §§ III.D.2, IV.A, VI.B

<sup>700</sup> *Supra* § VI.B.

<sup>701</sup> *Supra* § IV.A.2.

<sup>702</sup> *Supra* §§ III.D.2, IV.A, VI.B.

<sup>703</sup> *Supra* §§ IV.A, VI.B.

<sup>704</sup> *Supra* §§ III.D.2, IV.A, VI.B.

<sup>705</sup> *Supra* §§ IV.B, VI.B.

with respect to reducing exacerbation due to interstitial lung disease risk.<sup>706</sup> The tentatively approved Yutrepia label instructs administering Yutrepia according to the INCREASE study's dosing regimen, which as detailed above achieved a statistically significant treatment effect with respect to reducing exacerbation due to interstitial lung disease risk.<sup>707</sup> Therefore, the demonstrated statistical significance of this treatment effect in the INCREASE study leads me to conclude that administration of Yutrepia to PH-ILD patients consistent with Yutrepia's tentatively approved label will result in individual PH-ILD patients more likely than not exhibiting a treatment effect that reduces the risk of an exacerbation due to interstitial lung disease.<sup>708</sup>

285. Dr. Channick asserts that physicians' purported inability "to measure a 'reduction' in exacerbations of interstitial lung disease when treating individual patients because, unlike in a clinical trial, there is no control group with which [physicians] may draw a comparison . . . is sufficient to defeat any allegations of . . . infringement of claim 6."<sup>709</sup> I disagree with Dr. Channick that infringing claim 6 requires such acts. What is critical with respect to claim 6 is that the INCREASE study identified methods of administering inhaled treprostinil that achieved statistically significant treatment effects, which are the methods that claim 6 is directed to, and Yutrepia's tentatively approved label instructs performing these methods.<sup>710</sup> Accordingly, I disagree that the acts Dr. Channick proposes are relevant to whether administration of Yutrepia to PH-ILD patients infringes claim 6.<sup>711</sup> That is at least because, as detailed above, Dr. Channick's proposed comparisons are not required by claim 6 in view of the INCREASE study's outcomes,

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<sup>706</sup> *Supra* § VI.C.

<sup>707</sup> *Supra* §§ III.D.2, IV.A, VI.C.

<sup>708</sup> *Supra* §§ III.D.2, IV.A, VI.C.

<sup>709</sup> Channick Reb. Rpt. ¶ 77.

<sup>710</sup> *Supra* §§ III.D.2, IV.A.

<sup>711</sup> Channick Reb. Rpt. ¶¶ 65-66.

and the tentatively approved Yutrepia label instructs administering Yutrepia consistent with the INCREASE study's dosing regimen.

286. It is my opinion that administering Yutrepia according to Yutrepia's tentatively approved labeling will directly infringe claim 6 of the '327 patent. Yutrepia's tentatively approved labeling relies on reported methods of administering inhaled treprostinil to PH-ILD patients that achieve statistically significant treatment effects with respect to reducing the risk of exacerbations due to interstitial lung disease.<sup>712</sup> Accordingly, it is more likely than not that patients administered Yutrepia consistent with its tentatively approved label will experience an inhaled treprostinil treatment effect with respect to reducing the risk of exacerbations due to interstitial lung disease that was reported by the INCREASE study.<sup>713</sup>

287. Dr. Channick asserts that "a POSA would not naturally conclude from [the INCREASE data] that Yutrepia™ (which has a different formulation than Tyvaso®) would necessarily result in the same reduction of disease exacerbations since it is a different drug."<sup>714</sup> I disagree that a POSA's reading would be so limited. Rather, a POSA would apply the findings from the INCREASE data relating to exacerbations due to interstitial lung disease to PH-ILD patients administered Yutrepia consistent with Yutrepia's tentatively approved label.<sup>715</sup>

288. As explained above, INCREASE reported a statistically significant treatment effect with respect reducing the risk of an exacerbation due to interstitial lung disease using at least three statistical methods: Fisher's exact test, the log-rank test from the Cox proportional hazards model,

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<sup>712</sup> *Supra* §§ III.D.2, IV.A.

<sup>713</sup> *Supra* §§ III.D.2, IV.A.

<sup>714</sup> Channick Reb. Rpt. ¶ 76.

<sup>715</sup> *Supra* §§ III.D.2, IV.A.

and the chi-square test.<sup>716</sup> The Fisher's exact test reported a p-value of  $P=0.02$ .<sup>717</sup> The log-rank test reported a p-value of  $P=0.0396$ .<sup>718</sup> The chi-square test reported a p-value of  $P=0.0180$ .<sup>719</sup>

289. Dr. Channick attempts to support his non-infringement position by asserting that “[t]he Yutrepia™ label never mentions exacerbations of the interstitial lung disease, let alone provides any instruction to measure this parameter” and that “when treating PH-ILD patients to improve exercise capacity, [he] would not measure reductions of exacerbations of the interstitial lung disease.”<sup>720</sup> However, claim 6 does not require that exacerbations due to interstitial lung disease be noted and recorded at all. Claim 6 is directed to methods of administering treprostinil that provide a statistically significant treatment effect with respect to reducing the risk of an exacerbation due to interstitial lung disease. Recording or noting exacerbations due to interstitial lung disease would not affect whether a patient experienced such a treatment effect, it would merely document it. Under Dr. Channick's interpretation, a reduction in the risk of an exacerbation due to interstitial lung disease would not occur unless noted or recorded. I disagree. That is because, as detailed above, administering Yutrepia according to its tentatively approved label would infringe claim 6.

**G. Liquidia's Yutrepia Will Infringe Claim 7**

**1. “The method of claim 1, wherein said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease.”**

290. Claim 7 depends from claim 1. As described above, administering Yutrepia according to Liquidia's proposed label will meet all of the limitations of the method of claim 1.

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<sup>716</sup> *Supra* § III.D.2.b.4.

<sup>717</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -796.

<sup>718</sup> Nathan 2021 Supplement (UTC\_PH-ILD\_112161) at -169.

<sup>719</sup> INCREASE CSR (UTC\_PH-ILD\_055371) at -469.

<sup>720</sup> Channick Reb. Rpt. ¶¶ 75, 77.

Claim 7 additionally requires that the “administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease.”

291. Dr. Channick asserts the “[INCREASE] publication merely describes past data of a different drug, which does not instruct healthcare providers to practice the steps outlined in claim 7.”<sup>721</sup> I disagree with Dr. Channick asserting that the INCREASE study’s clinical worsening event due to interstitial lung disease outcomes do not inform Yutrepia outcomes. That is wrong for at least two reasons that I detailed above.<sup>722</sup> First, the Yutrepia sNDA for the PH-ILD indication relies entirely on the INCREASE study for evidence of clinical efficacy in PH-ILD patients, which is consistent with the tentatively approved Yutrepia label that only recites clinical support for the listed PH-ILD indication as the INCREASE study.<sup>723</sup> Therefore, as I have been informed by counsel, Yutrepia is bound by its label with respect to the PH-ILD indication, and Yutrepia necessarily is administered according to its label—i.e., consistent with the INCREASE study—and thus necessarily performs according to the INCREASE study.<sup>724</sup> That includes the statistically significant treatment effects with respect to reducing the risk of clinical worsening event due to interstitial lung disease, which as discussed above and herein are at least evidenced by the log-rank test analysis that was reported by the INCREASE publication and that is expressly recited on Yutrepia’s tentatively approved label.<sup>725</sup> I note the foregoing applies equally to Asserted Claim 8 that I address below.<sup>726</sup>

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<sup>721</sup> Channick Reb. Rpt. ¶ 82.

<sup>722</sup> *Supra* §§ VI.B-C.

<sup>723</sup> *Supra* § VI.B.

<sup>724</sup> *Supra* § VI.B.

<sup>725</sup> *Supra* §§ III.D.2, VI.B.

<sup>726</sup> *Infra* § VII.H.

292. Second, as far as I am aware there is no scientific basis for Dr. Channick's attempts to disassociate Yutrepia from the INCREASE study's outcomes.<sup>727</sup> And further, Dr. Channick's opinions in this regard are directly contrary to Liquidia's representations, including those made to FDA to obtain the PH-ILD indication for its Yutrepia product.<sup>728</sup> As explained above, because treprostinil is Yutrepia's only active ingredient and because Liquidia relies on INCREASE to support approval of its own product, the INCREASE study is sufficient evidence that administering Yutrepia to patients with PH-ILD will more likely than not exhibit the treatment effects that the INCREASE study reported.<sup>729</sup> Liquidia has also asserted that Yutrepia is biocomparable (satisfying the criteria for bioequivalence ) with Tyvaso through its LTI-102 study, and Yutrepia's label instructs administering Yutrepia consistent with the INCREASE study.<sup>730</sup> Accordingly, in view of the INCREASE study, LTI-102, and Yutrepia's tentatively approved label, I have not seen persuasive evidence or reasoning from Dr. Channick to believe that Yutrepia will not meet or exceed the INCREASE study outcomes with respect to reducing risk of clinical worsening events due to interstitial lung disease.<sup>731</sup> In fact, that is what Liquidia's CMO has admitted and the position Liquidia takes publicly and in its proposed marketing materials.<sup>732</sup> I note the foregoing applies equally to Asserted Claim 8 that I address below.<sup>733</sup>

293. Also, as detailed above, claim 7 distinguishes methods of administering inhaled treprostinil to PH-ILD patients that achieve (i.e., provide) a treatment effect at the population level

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<sup>727</sup> *Supra* § VI.B.

<sup>728</sup> *Supra* § VI.B.

<sup>729</sup> *Supra* §§ III.D.2, IV.A, VI.B.

<sup>730</sup> *Supra* §§ IV.A, VI.B.

<sup>731</sup> *Supra* §§ III.D.2, IV.A, VI.B.

<sup>732</sup> *Supra* §§ IV.B, VI.B.

<sup>733</sup> *Infra* § VII.H.

with respect to reducing clinical worsening events due to interstitial lung disease risk.<sup>734</sup> The tentatively approved Yutrepia label instructs administering Yutrepia according to the INCREASE study's dosing regimen, which as detailed above achieved a statistically significant treatment effect with respect to reducing clinical worsening events due to interstitial lung disease risk.<sup>735</sup> Therefore, the demonstrated statistical significance of this treatment effect in the INCREASE study leads me to conclude that administration of Yutrepia to PH-ILD patients consistent with Yutrepia's tentatively approved label will result in individual PH-ILD patients more likely than not exhibiting a treatment effect that reduces the risk of clinical worsening events due to interstitial lung disease.<sup>736</sup> As detailed above, I therefore disagree with Dr. Channick that his Rebuttal Report's discussion under § V.B.1 applies in any way to claim 7 or that infringing claim 7 "requires measuring clinical worsening events due to ILD, aggregating data from multiple patients and performing statistical analyses."<sup>737</sup> What is critical with respect to claim 7 is that the INCREASE study identified methods of administering inhaled treprostinil that achieved statistically significant treatment effects, which are the methods that claim 7 is directed to, and Yutrepia's tentatively approved label instructs performing these methods. Accordingly, I disagree that the acts Dr. Channick proposes are relevant whether administering of Yutrepia to PH-ILD patients infringes claim 7.<sup>738</sup> This also includes "measure a 'reduction' in clinical worsening events when treating individual patients" or drawing comparisons to a control group.<sup>739</sup> That is at least because, as detailed above, Dr. Channick's proposed acts are not required by claim 7 in view of the

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<sup>734</sup> *Supra* § VI.C.

<sup>735</sup> *Supra* §§ III.D.2, IV.A, VI.C.

<sup>736</sup> *Supra* §§ III.D.2, IV.A, VI.C.

<sup>737</sup> Channick Reb. Rpt. ¶80.

<sup>738</sup> Channick Reb. Rpt. ¶¶ 65-66.

<sup>739</sup> Channick Reb. Rpt. ¶ 81.

INCREASE study's outcomes, and the tentatively approved Yutrepia label instructs administering Yutrepia consistent with the INCREASE study's dosing regimen. I note the foregoing applies equally to Asserted Claim 8 that I address below.<sup>740</sup>

294. It is my opinion that administering Yutrepia according to Yutrepia's tentatively approved labeling will infringe claim 7 of the '327 patent. This is clear because the Yutrepia tentatively approved labeling and the INCREASE study on which the proposed labeling relies report methods of administering inhaled treprostinil to PH-ILD patients that achieve a statistically significant treatment effect with respect to reducing the risk of clinical worsening events due to interstitial lung disease.<sup>741</sup> Accordingly, it is more likely than not that patients administered Yutrepia consistent with its tentatively approved label will experience an inhaled treprostinil treatment effect with respect to reducing the risk of clinical worsening events due to interstitial lung disease that was reported by the INCREASE study.<sup>742</sup>

295. Dr. Channick asserts that the "[INCREASE] publication merely describes past data of a different drug, which does not instruct healthcare providers to practice the steps outlined in claim 7."<sup>743</sup> I disagree that a POSA's reading would be so limited. Rather, a POSA would apply the findings from the INCREASE trial relating to clinical worsening due to interstitial lung disease to PH-ILD patients administered Yutrepia consistent with Yutrepia's tentatively approved label.<sup>744</sup>

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<sup>740</sup> *Infra* § VII.H.

<sup>741</sup> *Supra* §§ III.D.2, IV.A.

<sup>742</sup> *Supra* §§ III.D.2, IV.A.

<sup>743</sup> Channick Reb. Rpt. ¶ 82.

<sup>744</sup> *Supra* §§ III.D.2, IV.A.

296. As explained above, INCREASE reported a statistically significant treatment effect with respect reducing the risk of clinical worsening events due to interstitial lung disease using at least a log-rank test.<sup>745</sup> The log-rank test reported a p-value of  $P=0.04$ .<sup>746</sup>

297. Furthermore, the tentatively approved Yutrepia label explicitly reports the INCREASE study's clinical worsening event outcomes, detailing that administering inhaled treprostinil to PH-ILD patients provided statistically significant treatment effects with respect to reducing the risk of clinical worsening events due to interstitial lung disease.<sup>747</sup> To evidence this, the tentatively approved Yutrepia label reports that a log-rank test yielded a p-value of  $p=0.041$ .<sup>748</sup>

298. Dr. Channick attempts to support his non-infringement position by asserting that “[t]o practice claim 7, healthcare providers and patients would need to monitor the clinical worsening events experienced due to interstitial lung disease and determine whether Yutrepia™ administration produces a statistically significant result.”<sup>749</sup> However, claim 7 does not require that clinical worsening events due to interstitial lung disease be noted or recorded at all. Claim 7 is directed to methods of administering treprostinil that provide a statistically significant treatment effect with respect to reducing the risk of clinical worsening events due to interstitial lung disease. Recording clinical worsening events due to interstitial lung disease would not affect whether a patient experienced such a treatment effect, it would merely document it. Under Dr. Channick's interpretation, a reduction in the risk of clinical worsening events due to interstitial lung disease would not occur unless noted or recorded. I disagree. That is because, as detailed above, administering Yutrepia according to its tentatively approved label would infringe claim 7.

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<sup>745</sup> *Supra* § III.D.2.b.3.

<sup>746</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -794.

<sup>747</sup> *Supra* § IV.A.

<sup>748</sup> Yutrepia Label (LIQ\_PH-ILD\_00126017) at-032-033.

<sup>749</sup> Channick Reb. Rpt. ¶ 80.

**H. Liquidia's Yutrepia Will Infringe Claim 8**

- 1. "The method of claim 7, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline."**

299. Claim 8 depends from claims 1 and 7. As described above, administering Yutrepia according to Liquidia's proposed label will meet all of the limitations of claims 1 and 7. Claim 8 additionally requires that the "the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline."

300. Dr. Channick asserts that he does "not believe a healthcare provider or a patient would directly infringe claim 7 based on the proposed Yutrepia™ label (or the publications and marketing materials not referenced in the label that Dr. Nathan cites)" and therefore is "of the opinion that they will not directly infringe claim 8."<sup>750</sup> I disagree. First, as detailed above, administering Yutrepia consistent with Yutrepia's tentatively approved label would more likely than not result in that patient experiencing the reduction in clinical worsening events due to interstitial lung disease risk treatment effect reported by the INCREASE study.<sup>751</sup> Moreover, the INCREASE study, in addition to reporting a statistically significant treatment effect with respect reducing the risk of clinical worsening events due to interstitial lung disease, further reported hospitalizations due to a cardiopulmonary indication and a decrease in 6MWD >15% from baseline were among the clinical worsening events due to interstitial lung disease observed at a certain frequency in both the treatment and placebo arms.<sup>752</sup> Moreover, when examining just the clinical worsening events of hospitalizations due to a cardiopulmonary indication and a decrease in 6MWD

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<sup>750</sup> Channick Reb. Rpt. ¶ 83.

<sup>751</sup> *Supra* §§ VII.B & VII.G.

<sup>752</sup> *Supra* § III.D.2.b.3; INCREASE publication (UTC\_PH-ILD\_010790) at -797.

>15% from baseline reported in the INCREASE publication, there was a statistically significant reduction by Fisher's exact test ( $p=0.021$ ).<sup>753</sup>

301. Furthermore, the tentatively approved Yutrepia label details the INCREASE study findings that administering inhaled treprostinil to PH-ILD patients provided statistically significant treatment effects with respect to reducing the risk of clinical worsening events due to interstitial lung disease, and it also expressly reports that hospitalizations due to a cardiopulmonary indication and a decrease in 6MWD >15% from baseline were among those that occurred with a certain frequency within the treatment and placebo arms of the INCREASE study.<sup>754</sup>

302. Therefore, administering Yutrepia according to its tentatively approved label would more likely than not result in that patient experiencing the reduction in clinical worsening events due to interstitial lung disease risk treatment effect reported by the INCREASE study for which the relevant clinical worsening events include at hospitalizations due to a cardiopulmonary indication or a decrease in 6MWD >15% from baseline.<sup>755</sup>

303. Therefore, it is my opinion that administering Yutrepia according to Yutrepia's proposed labeling will infringe claim 8. This is clear because Yutrepia's tentatively approved labeling and the INCREASE study on which the tentatively approved labeling relies report

<sup>753</sup> Calculation of Fisher Exact Test using Stata version 18.5:

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. // Clinical worsening: hospitalization and/or 6MWD decrease of >15%
. tabi 31 132 \ 50 113, exact
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row	col		Total
	1	2	
1	31	132	163
2	50	113	163
Total	81	245	326

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Fisher's exact = 0.021
1-sided Fisher's exact = 0.010
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<sup>754</sup> *Supra* § IV.A.3.b; Yutrepia Label (LIQ\_PH-ILD\_00126017) at-032-033.

<sup>755</sup> *Supra* § VI.B.

methods of administering inhaled treprostinil to PH-ILD patients that achieve a statistically significant treatment effect with respect to reducing the risk of clinical worsening events due to interstitial lung disease in which the comprising clinical worsening events were at least hospitalization for cardiopulmonary indication or a decrease in 6MWD >15% compared to baseline.

**I. Liquidia's Yutrepia Will Infringe Claim 9**

**1. "The method of claim 1, wherein said administering provides a statistically significant improves of forced vital capacity (FVC) in the patient after 8 weeks, 12 weeks or 16 weeks."**

304. Claim 9 depends from claim 1. As described above, administering Yutrepia according to Liquidia's proposed label will meet all of the limitations of claim 1. Claim 9 additionally requires that the "administering provides a statistically significant improves of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks." I also understand that because the timepoint limitations are listed in the alternative ("8 weeks, 12 weeks, *or* 16 weeks") that means acts satisfying any one of those timepoints is sufficient to infringe claim 9, i.e., infringing acts do not require satisfying all three time points.

305. Dr. Channick asserts that "a healthcare provider or patient would have no reason to expect that Yutrepia™ (which is a different formulation from Tyvaso®) would produce these results."<sup>756</sup> Dr. Channick also asserts that the INCREASE study and its post-hoc analyses merely describe past FVC measurements of a different drug, which does not instruct healthcare providers to practice the steps outlined in claims 9 or 10."<sup>757</sup> I disagree with Dr. Channick that a direct infringer would need to "*expect*" whether they are infringing in the way Dr. Channick suggests is necessary, and I also disagree with Dr. Channick's assertion that the INCREASE study's FVC

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<sup>756</sup> Channick Reb. Rpt. ¶ 65.

<sup>757</sup> Channick Reb. Rpt. ¶ 88.

outcomes do not inform Yutrepia outcomes. That is wrong for at least two reasons that I detailed above.<sup>758</sup> First, the Yutrepia sNDA for the PH-ILD indication relies entirely on the INCREASE study for evidence of clinical efficacy in PH-ILD patients, which is consistent with the tentatively approved Yutrepia label that only recites clinical support for the listed PH-ILD indication as the INCREASE study.<sup>759</sup> Therefore, as I have been informed by counsel, Yutrepia is bound by its label with respect to the PH-ILD indication, and for the purpose of considering infringement in this case Yutrepia is administered according to its label—i.e., consistent with the INCREASE study—and thus necessarily performs according to the INCREASE study.<sup>760</sup> That includes the statistically significant treatment effects with respect to FVC at 8 and 16 weeks after initiation of inhaled treprostinil, which as discussed above and herein are at least evidenced by the MMRM model analyses that were reported by the INCREASE publication and published post-hoc analyses.<sup>761</sup> Although these data do not appear to be recited on Yutrepia’s tentatively approved label, that label still instructs administering Yutrepia consistent with methods that the INCREASE study and post-hoc analyses demonstrated provided the statistically significant treatment effects in PH-ILD patients. I note the foregoing applies equally to Asserted Claim 10 that I address below.<sup>762</sup>

306. Second, as far as I am aware there is no scientific basis for Dr. Channick’s attempts to disassociate Yutrepia from the INCREASE study’s outcomes.<sup>763</sup> And further, Dr. Channick’s opinions in this regard are directly contrary to Liquidia’s representations, including those made to FDA to obtain the PH-ILD indication for its Yutrepia product.<sup>764</sup> As explained above, because

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<sup>758</sup> *Supra* §§ VI.B-C.

<sup>759</sup> *Supra* § VI.B.

<sup>760</sup> *Supra* § VI.B.

<sup>761</sup> *Supra* §§ III.D.2, VI.B.

<sup>762</sup> *Infra* § VII.J.

<sup>763</sup> *Supra* § VI.B.

<sup>764</sup> *Supra* § VI.B.

treprostinil is Yutrepia's only active ingredient and because Liquidia relies on INCREASE to support approval of its own product, the INCREASE study is sufficient evidence that administering Yutrepia to patients with PH-ILD will more likely than not exhibit the treatment effects that the INCREASE study reported and will do so at a magnitude equal or greater than what was reported.<sup>765</sup> Liquidia has also asserted that Yutrepia is biocomparable (satisfying the criteria for bioequivalence) with Tyvaso through its LTI-102 study, and Yutrepia's label instructs administering Yutrepia consistent with the INCREASE study.<sup>766</sup> Accordingly, in view of the INCREASE study, LTI-102, and Yutrepia's tentatively approved label, I have not seen persuasive evidence or reasoning from Dr. Channick to believe that Yutrepia will not meet or exceed the INCREASE study FVC outcomes.<sup>767</sup> In fact, that is what Liquidia's CMO has admitted. I note the foregoing applies equally to Asserted Claim 10 that I address below.<sup>768</sup>

307. Also, as detailed above, claim 9 distinguishes methods of administering inhaled treprostinil to PH-ILD patients that achieve (i.e., provide) an FVC treatment effect at the population level at the respectively recited timepoints.<sup>769</sup> The tentatively approved Yutrepia label instructs administering Yutrepia according to the INCREASE study's dosing regimen, which as detailed above achieved a statistically significant FVC treatment effect at 8 and 16 weeks.<sup>770</sup> Therefore, the demonstrated statistical significance of these FVC treatment effects in the INCREASE study leads me to conclude that administration of Yutrepia to PH-ILD patients

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<sup>765</sup> *Supra* §§ III.D.2, IV.A, VI.B.

<sup>766</sup> *Supra* §§ IV.A, VI.B.

<sup>767</sup> *Supra* §§ III.D.2, IV.A, VI.B.

<sup>768</sup> *Infra* § VII.J.

<sup>769</sup> *Supra* § VI.C.

<sup>770</sup> *Supra* §§ III.D.2, IV.A, VI.C.

consistent with Yutrepia's tentatively approved label will result in individual PH-ILD patients more likely than not exhibiting the 8-week or 16-week treatment effects identified in claim 9.<sup>771</sup>

308. As detailed above, I disagree with Dr. Channick that infringing claim 9 requires:

[A] doctor or patient measure FVC at baseline and again at least 8 weeks after administering inhaled treprostinil, and then achieve a statistically significant result. Claim 10 adds the requirement that the improvement in the patient must be at least 20 ml after at least 8 weeks of administering the drug.<sup>772</sup>

The INCREASE study identified methods of administering inhaled treprostinil that achieved statistically significant treatment effects, which are the methods that claim 9 is directed to, and Yutrepia's tentatively approved label instructs performing these methods.<sup>773</sup> Accordingly, I disagree with Dr. Channick's position that infringement of claim 9 requires any of the above-quoted acts.<sup>774</sup> That is at least because, as detailed above, those acts are not required by claim 9 in view of the INCREASE study's outcomes, and the tentatively approved Yutrepia label instructs administering Yutrepia consistent with the INCREASE study's dosing regimen. I note the foregoing applies equally as relevant to Asserted Claim 10.<sup>775</sup>

309. It is my opinion that administering Yutrepia according to Yutrepia's tentatively approved label will infringe claim 9 of the '327 patent. Yutrepia's tentatively approved labeling relies on reported methods of administering inhaled treprostinil to PH-ILD patients that achieve statistically significant treatment effects with respect to % predicted FVC after 8 weeks and 16 weeks as well as a statistically significant improvement in absolute FVC in the IIP and IPF subpopulations after 16 weeks as claimed.<sup>776</sup> Accordingly, it is more likely than not that PH-ILD

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<sup>771</sup> *Supra* §§ III.D.2, IV.A.

<sup>772</sup> *Supra* § VI.C; Channick Reb. Rpt. ¶ 85.

<sup>773</sup> *Supra* §§ III.D.2, IV.A, VI.C.

<sup>774</sup> Channick Reb. Rpt. ¶¶ 65-66.

<sup>775</sup> *Infra* § VII.J.

<sup>776</sup> *Supra* §§ III.D.2, IV.A.

patients, especially those within the IIP and IPF subpopulations, administered Yutrepia consistent with its tentatively approved label will experience an inhaled treprostinil treatment effect with respect to % predicted FVC after 8 weeks and 16 weeks as well as a statistically significant improvement in absolute FVC in the IIP and IPF subpopulations after 16 weeks that were reported by the INCREASE study or its post hoc analyses.<sup>777</sup>

310. Dr. Channick asserts that the INCREASE data “merely describe past FVC measurements of a different drug, which does not instruct healthcare providers to practice the steps outlined in claims 9 or 10” with respect to Yutrepia.<sup>778</sup> I disagree that a POSA’s reading would be so limited. Rather, a POSA would apply the findings from the INCREASE data relating to FVC to PH-ILD patients administered Yutrepia consistent with Yutrepia’s tentatively approved label.<sup>779</sup>

311. As explained above, INCREASE reported statistically significant treatment effects with respect to FVC, specifically improvements of % predicted FVC after 8 weeks and 16 weeks, using an MMRM model.<sup>780</sup> This analysis resulted in a p-value of P=0.01 at week 8 and P=0.03 at week 16.<sup>781</sup>

312. As explained above, the INCREASE post hoc analyses reported statistically significant treatment effects with respect to absolute FVC in the IIP and IPF subpopulations after 16 weeks using the MMRM model.<sup>782</sup> The resulting analysis reported a p-value of p=0.023 in the IIP subpopulation after 16 weeks and p=0.011 in the IPF subpopulation after 16 weeks.<sup>783</sup>

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<sup>777</sup> *Supra* §§ III.D.2, IV.A.

<sup>778</sup> Channick Reb. Rpt. ¶ 88.

<sup>779</sup> *Supra* §§ III.D.2, IV.A.

<sup>780</sup> Nathan 2021 (UTC\_PH-ILD\_147114) at -117.

<sup>781</sup> INCREASE publication (UTC\_PH-ILD\_010790) at -825.

<sup>782</sup> Nathan 2021 (UTC\_PH-ILD\_147114) at -117.

<sup>783</sup> Nathan 2021 (UTC\_PH-ILD\_147114) at -117-119.

313. The INCREASE post hoc analysis also reported statistically significant treatment effects with respect to % predicted FVC in the IIP and IPF subpopulations after 8 and 16 weeks. Regarding the IIP subpopulation, the resulting analysis reported a p-value of  $p=0.037$  after 8 weeks and  $p=0.0096$  after 16 weeks.<sup>784</sup> Regarding the IPF subpopulation, the resulting analysis reported a p-value of  $p=0.038$  after 8 weeks and  $p=0.015$  after 16 weeks.<sup>785</sup>

314. Dr. Channick attempts to support his non-infringement position by asserting that “[t]he proposed Yutrepia™ label makes no mention of FVC, let alone provide an instruction or directive to a healthcare provider to measure FVC during the course of Yutrepia™ treatment of PH-ILD patents” and that “FVC is not typically assessed outside of a clinical trial, let alone assessed at the claimed intervals.”<sup>786</sup> However, claim 9 does not require that FVC be measured at all. Claim 9 is directed to methods of administering treprostinil that provide a statistically significant treatment effect with respect to FVC. Measuring FVC would not affect whether a patient experienced such a treatment effect, it would merely document it. Under Dr. Channick’s interpretation, an improvement in FVC would not occur unless measured. I disagree. That is because, as detailed above, administering Yutrepia according to its tentatively approved label would infringe claim 9.

**J. Liquidia’s Yutrepia Will Infringe Claim 10**

1. “The method of claim 9, wherein said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks.”

315. Claim 10 depends from claims 1 and 9. As described above, administering Yutrepia according to Liquidia’s proposed label will meet all of the limitations of claims 1 and 9. Claim 10

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<sup>784</sup> Nathan 2021 (UTC\_PH-ILD\_147114) at -118.

<sup>785</sup> Nathan 2021 (UTC\_PH-ILD\_147114) at -118-119.

<sup>786</sup> Channick Reb. Rpt. ¶¶ 87-89.

additionally requires that the “administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks.” I also understand that because the timepoint limitations are listed in the alternative (“8 weeks, 12 weeks, *or* 16 weeks”) that means acts satisfying any one of those timepoints is sufficient to infringe claim 10, i.e., infringing acts do not require satisfying all three time points.

316. It is my opinion that administering Yutrepia according to Yutrepia’s tentatively approved labeling will infringe claim 10 of the ’327 patent. This is clear because Yutrepia’s tentatively approved labeling relies on reported methods of administering inhaled treprostinil to PH-ILD patients that yield improvements of FVC by at least 20 ml in the IIP and IPF subpopulations after 16 weeks as claimed.<sup>787</sup> Accordingly, it is more likely than not that PH-ILD patients, especially those within the IIP and IPF subpopulations, administered Yutrepia consistent with its tentatively approved label will generally experience the beneficial effect of improvements of FVC by at least 20 ml after 16 weeks that was reported by the INCREASE study or its post hoc analyses.<sup>788</sup>

317. Dr. Channick asserts that the INCREASE data “merely describe past FVC measurements of a different drug, which does not instruct healthcare providers to practice the steps outlined in claims 9 or 10” with respect to Yutrepia.<sup>789</sup> I disagree that a POSA’s reading would be so limited. Rather, a POSA would apply the findings from the INCREASE data relating to FVC to PH-ILD patients administered Yutrepia consistent with Yutrepia’s tentatively approved label.<sup>790</sup>

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<sup>787</sup> *Supra* §§ III.D.2, IV.A.

<sup>788</sup> *Supra* §§ III.D.2, IV.A.

<sup>789</sup> Channick Reb. Rpt. ¶ 88.

<sup>790</sup> *Supra* § VII.I.

318. Dr. Channick asserts that the INCREASE data “merely describe past FVC measurements of a different drug, which does not instruct healthcare providers to practice the steps outlined in claims 9 or 10” with respect to Yutrepia.<sup>791</sup> I disagree that a POSA’s reading would be so limited. Rather, a POSA would apply the findings from the INCREASE data relating to FVC to PH-ILD patients administered Yutrepia consistent with Yutrepia’s tentatively approved label.<sup>792</sup>

319. As explained above, INCREASE reported improvements of FVC by at least 20 ml in the IIP and IPF subpopulations after 16 weeks using an MMRM model.<sup>793</sup> These analyses reported an improvement in FVC of 108.2 mL in the IIP subpopulation after 16 weeks and 168.5 mL in the IPF subpopulation after 16 weeks.<sup>794</sup>

320. Dr. Channick attempts to support his non-infringement position by asserting that “[t]he proposed Yutrepia™ label makes no mention of FVC, let alone provide an instruction or directive to a healthcare provider to measure FVC during the course of Yutrepia™ treatment of PH-ILD patents” and that “FVC is not typically assessed outside of a clinical trial, let alone assessed at the claimed intervals.”<sup>795</sup> However, claim 10 does not require that FVC be measured at all. Claim 10 is directed to methods of administering treprostinil that provide a statistically significant treatment effect with respect to FVC. Measuring FVC would not affect whether a patient experienced such a treatment effect, it would merely document it. Under Dr. Channick’s interpretation, an improvement in FVC would not occur unless measured. I disagree. That is because, as detailed above, administering Yutrepia according to its tentatively approved label would infringe claim 10.

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<sup>791</sup> Channick Reb. Rpt. ¶ 88.

<sup>792</sup> *Supra* §§ III.D.2, IV.A.

<sup>793</sup> Nathan 2021 (UTC\_PH-ILD\_147114) at -117.

<sup>794</sup> Nathan 2021 (UTC\_PH-ILD\_147114) at -117-119.

<sup>795</sup> Channick Reb. Rpt. ¶¶ 87-89.

**K. Liquidia's Yutrepia Will Infringe Claim 11**

**1. "The method of claim 1, wherein said administering is performed by a pulsed inhalation device."**

321. Claim 11 depends from claim 1. As described above, administering Yutrepia according to Liquidia's proposed label will meet all of the limitations of the method of claim 1. Claim 11 additionally requires that the "administering is performed by a pulsed inhalation device."

322. I understand that the Court construed the term "pulsed inhalation device" in this claim as "a device that provides for non-continuous inhaled drug delivery."

323. Dr. Channick does not dispute infringement of claim 11 separate from his opinions regarding claim 1. As noted above, I disagree with Dr. Channick's opinions regarding claim 1 because it is my opinion that administration of Yutrepia according to Liquidia's proposed label will meet all the limitations of claim 1.<sup>796</sup> I have also reviewed Dr. Nathan's opening report and agree with his infringement analysis regarding claim 11.<sup>797</sup>

**L. Liquidia's Yutrepia Will Infringe Claim 14**

**1. "The method of claim 11, wherein the pulsed inhalation device is a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof."**

324. Claim 14 depends from claims 1 and 11. As described above, administering Yutrepia according to Liquidia's proposed label will meet all of the limitations of claim 1. Claim 14 additionally requires that the "the pulsed inhalation device is a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof."

325. Dr. Channick does not dispute infringement of claim 14 separate from his opinions regarding claim 1. As noted above, I disagree with Dr. Channick's opinions regarding claim 1

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<sup>796</sup> *Supra* § VII.A.

<sup>797</sup> Nathan Op. Rpt. § VI.A.11.

because it is my opinion that administration of Yutrepia according to Liquidia's proposed label will meet all the limitations of claim 1.<sup>798</sup> I have also reviewed Dr. Nathan's opening report and agree with his infringement analysis regarding claim 14.<sup>799</sup>

**M. Liquidia's Yutrepia Will Infringe Claim 15**

**1. "The method of claim 1, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15 µg to 100 µg."**

326. Claim 15 depends from claim 1. As described above, administering Yutrepia according to Liquidia's proposed label will meet all of the limitations of claim 1. Claim 15 additionally requires that the "the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15 µg to 100 µg."

327. Dr. Channick does not dispute infringement of claim 15 separate from his opinions regarding claim 1. As noted above, I disagree with Dr. Channick's opinions regarding claim 1 because it is my opinion that administration of Yutrepia according to Liquidia's proposed label will meet all the limitations of claim 1.<sup>800</sup> I have also reviewed Dr. Nathan's opening report and agree with his infringement analysis regarding claim 15.<sup>801</sup>

**N. Liquidia's Yutrepia Will Infringe Claim 16**

**1. "The method of claim 15, wherein the single inhalation administration event does not exceed 15 breaths by the patient."**

328. Claim 16 depends from claims 1 and 15. As described above, administering Yutrepia according to Liquidia's proposed label will meet all of the limitations of claim 1. Claim

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<sup>798</sup> *Supra* § VII.A.

<sup>799</sup> Nathan Op. Rpt. § VI.A.12.

<sup>800</sup> *Supra* § VII.A.

<sup>801</sup> Nathan Op. Rpt. § VI.A.13.

16 additionally requires that the “the single inhalation administration event does not exceed 15 breaths by the patient.”

329. Dr. Channick does not dispute infringement of claim 16 separate from his opinions regarding claim 1. As noted above, I disagree with Dr. Channick’s opinions regarding claim 1 because it is my opinion that administration of Yutrepia according to Liquidia’s proposed label will meet all the limitations of claim 1.<sup>802</sup> I have also reviewed Dr. Nathan’s opening report and agree with his infringement analysis regarding claim 16.<sup>803</sup>

**O. The ASCENT Study Infringes the Asserted Claims**

330. Dr. Channick asserts that the ASCENT study cannot infringe Asserted Claims 2, 4, 6, 7, and 9 because the claims require a “‘statistically significant’ result.”<sup>804</sup> Dr. Channick asserts that infringing these claims requires that a “healthcare provider must take the additional steps of treating multiple patients, aggregating the data collected from the patients, and then running a statistical analysis,” while the ASCENT clinical research protocol does not instruct these extra steps.<sup>805</sup> I disagree with Dr. Channick for the reasons I detail above.<sup>806</sup> Claims 2, 4, 6, 7, and 9 identify methods of administering inhaled treprostinil in PH-ILD patients that achieve statistically significant treatment effects, and the INCREASE study has already established that administering treprostinil to PH-ILD patients provides statistically significant treatment effects with respect to 6MWD, plasma NT-proBNP concentration, risk of exacerbations due to interstitial lung disease, risk of clinical worsening events due to interstitial lung disease, and forced vital capacity.<sup>807</sup>

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<sup>802</sup> *Supra* § VII.A.

<sup>803</sup> Nathan Op. Rpt. § VI.A.14.

<sup>804</sup> Channick Reb. Rpt. ¶ 157.

<sup>805</sup> Channick Reb. Rpt. ¶ 158.

<sup>806</sup> *Supra* §§ VI.B-C.

<sup>807</sup> *Supra* §§ III.D.2, VI.B-C; *see generally* INCREASE publication (UTC\_PH-ILD\_010790); *see generally* INCREASE Protocol (UTC\_PH-ILD\_145360); *see generally* Nathan 2021 (UTC\_PH-ILD\_147114).

331. As detailed above, the ASCENT study administers Yutrepia to PH-ILD patients consistent with the INCREASE study, and ultimately proposes administering dosages that were higher than what was administered in INCREASE.<sup>808</sup> Likewise, the ASCENT study's dosing protocol is nearly identical to the dosing protocol provided on Yutrepia's tentatively approved label.<sup>809</sup> Both the Yutrepia label and the ASCENT protocol specify administration of Yutrepia 3 to 5 times per day.<sup>810</sup> Both also instruct taking two breaths per capsule.<sup>811</sup> Both also instruct starting at a capsule strength of 26.5 mcg.<sup>812</sup> Both also instruct achieving a target maintenance dosage of 79.5 mcg or higher four times per day.<sup>813</sup> Accordingly the methods of administering Yutrepia to the subjects of the ASCENT study set forth in the ASCENT study's clinical research protocol are more likely than not to yield the inhaled treprostinil treatment effects recited in Asserted Claims 2, 4, 6, 7, and 9.<sup>814</sup> Therefore, Dr. Channick's "additional steps" are not required in view of the INCREASE study, Yutrepia's tentatively approved label, and the ASCENT clinical research protocol.<sup>815</sup>

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<sup>808</sup> *Supra* § III.D.2, IV.C.; *see generally* First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607); *see generally* INCREASE publication (UTC\_PH-ILD\_010790); *see generally* INCREASE Protocol (UTC\_PH-ILD\_145360); *see generally* Nathan 2021 (UTC\_PH-ILD\_147114).

<sup>809</sup> *Supra* §§ IV.A, IV.C; *see generally* First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607); Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022, -026-027.

<sup>810</sup> *Supra* §§ IV.A, IV.C; First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -633; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022, -026-027.

<sup>811</sup> *Supra* §§ IV.A, IV.C; First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -668; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022.

<sup>812</sup> *Supra* §§ IV.A, IV.C; First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -633; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022.

<sup>813</sup> *Supra* §§ IV.A, IV.C; First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -633; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022.

<sup>814</sup> *Supra* §§ III.D.2, IV.A, IV.C, VI.B-C; First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -633; Yutrepia Label (LIQ\_PH-ILD\_00126017) at -021-022; *see generally* INCREASE publication (UTC\_PH-ILD\_010790); *see generally* INCREASE Protocol (UTC\_PH-ILD\_145360); *see generally* Nathan 2021 (UTC\_PH-ILD\_147114).

<sup>815</sup> Channick Reb. Rpt. ¶ 157-158.

332. It is therefore my opinion that physicians and patients have and will directly infringe each of the Asserted Claims of the '327 patent by administering Yutrepia during the ASCENT study according to that study's dosing protocol (which is nearly identical to Liquidia's proposed labeling) because Yutrepia's tentatively approved labeling, and the INCREASE study on which Yutrepia's tentatively approved labeling relies, reported methods of administering inhaled treprostinil that provide the recited statistically significant treatment effects and are more likely than not to achieve the recited outcomes.<sup>816</sup> Accordingly, it is more likely than not that on average patients administered Yutrepia during the ASCENT study will generally experience the beneficial effects described in the Yutrepia label and the INCREASE study.

333. The inclusion criteria defining the patient population for the ASCENT study are also nearly identical to the patient population included in the INCREASE study. Both confirmed presence of ILD based on CT imaging.<sup>817</sup> Both confirmed the presence of Group 3 PH with inclusion criteria of PVR > 3 Wood units and wedge pressure  $\leq$  15 mm Hg as measured by right heart catheterization.<sup>818</sup> And INCREASE had an inclusion criteria of mPAP  $\geq$  25 mm Hg, while ASCENT had an inclusion criteria of mPAP  $\geq$  30 mm Hg as measured by right heart catheterization.<sup>819</sup>

334. While I have not been asked to determine whether the safe harbor applies to the ASCENT study, I note that Liquidia's CMO had indicated that the purpose of the study is to "showcase its product profile."<sup>820</sup> He also stated that Liquidia is conducting the ASCENT study because "it is important to showcase [Yutrepia] in a clinical trial because it's actually never been

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<sup>816</sup> *Supra* §§ IV.C, VI.B.2., VI.C, VII.A-VII.N.

<sup>817</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -612.

<sup>818</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -612.

<sup>819</sup> First Amended ASCENT Protocol (LIQ\_PH-ILD\_00147607) at -612.

<sup>820</sup> Rajeev Saggat Dep. Tr. at 79:22-83:12

run. And so to run a prospective open-label study will allow providers to gain additional experience with Yutrepia, specifically in that population, ... .”<sup>821</sup> And he noted that “ASCENT has no regulatory status in regards to the FDA’s consideration for approval or indication of PH-ILD for Yutrepia.”<sup>822</sup> Based on these statements, it appears to me that the ASCENT study is undertaken primarily as a marketing exercise in order to showcase to potential prescribing physicians how Yutrepia will work in patients if and when it is approved.

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<sup>821</sup> Rajeev Saggar Dep. Tr. at 81:3-8.

<sup>822</sup> Rajeev Saggar Dep. Tr. at 80:10-13.

I declare under penalty of perjury that the foregoing is true and correct.

DATED: 21 February 2025

R. A. Thisted

**Ronald A. Thisted, Ph.D.**

# EXHIBIT D

### MATERIALS CONSIDERED

Patent Documents	
'327 patent	U.S. Patent No. 11,826,327 (UTC PH-ILD_005310)
Expert Reports/Declarations	
Channick Op. Rept.	2024-12-20 Expert Report of Dr. Richard Channick
Channick Reb. Rpt.	2025-01-23 Rebuttal Expert Report of Dr. Richard Channick
Nathan PI Decl.	2024-02-26 D.I. 28 Declaration of Steven D. Nathan, M.D.
Nathan Op. Rpt.	2024-12-20 Expert Report of Steven D. Nathan, M.D.
Thisted Reb. Rpt.	2025-01-23 Rebuttal Report of Ronald A. Thisted, Ph.D.
Litigation Materials	
Deng Dep. Tr.	2024-11-12 Chunqin Deng Deposition Transcript
	2024-12-27 Chunqin Deng Errata
Rajeev Saggar Dep. Tr.	2024-10-16 Rajeev Saggar Deposition Transcript
	2024-12-09 Rajeev Saggar Errata
	D.I. 136 (2024-10-08 UTC's 30(b)(6) Notice of Deposition to Liquidia)
Literature	
Faria-Urbina 2018	UTC PH-ILD_009936
Faria-Urbina 2018 Suppl. Materials	UTC PH-ILD_219375
Nathan 2021	UTC PH-ILD_147114
Nathan 2021 Supplement	UTC PH-ILD_112161
Roscigno 2021	UTC PH-ILD_010665
Thabane 2013	UTC PH-ILD_227534
Other	
2009 Tyvaso Label	UTC PH-ILD_010692
2022 Tyvaso DPI Label	UTC PH-ILD_010709
2022 Tyvaso Label	UTC PH-ILD_005268
Amended Proposed Label	LIQ PH-ILD_00091129
Amendment Cover Letter	LIQ PH-ILD_00091022
ASCENT at Clinical Trials	UTC PH-ILD_000395
ASCENT Protocol	LIQ PH-ILD_00124867
Beth Goldstein, Sci. Pol'y Analyst, U.S. Food & Drug Admin., Overview of the 505(b)(2) Regulatory Pathway for New Drug Applications	UTC PH-ILD_227379
FDA GFI 2001 Statistical Approaches to Establishing BE	UTC PH-ILD_227453
FDA Draft GFI 2022 Statistical Approaches to Establishing BE	UTC PH-ILD_227501
FDA Response	LIQ PH-ILD_00120424

FDA's Labeling Resources for Human Prescription Drugs   FDA.pdf (7-Feb-2025)	UTC_PH-ILD_227394
Feb. 24, 2020 press release announcing INCREASE results	UTC_LIQ00063612
First Amended ASCENT Protocol	LIQ_PH-ILD_00147607
INCREASE CSR	UTC_PH-ILD_055371
INCREASE Protocol	UTC_PH-ILD_145360
INCREASE publication	UTC_PH-ILD_010790
IND 129819 Application	LIQ_PH-ILD_00022883
IND 129819 SN0001 Cover Letter	LIQ_PH-ILD_00022878
June 6, 2017 Correspondence	LIQ_PH-ILD_00046141
March 13, 2024 Press Release	LIQ_PH-ILD_00143338
May 11, 2017 Correspondence	LIQ_PH-ILD_00046101
May 20, 2023 PH-ILD Advisory Board	LIQ_PH-ILD_00122627
Meeting Request Cover Letter	LIQ_PH-ILD_00134042
National Cancer Institute 2025	UTC_PH-ILD_227452
Nov. 2020 LIQ861 Steering Committee Meeting	LIQ_PH-ILD_00113881
Original 505(b)(2) Application	LIQ_PH-ILD_00046054
Original NDA 213005 § 2.2	LIQ_PH-ILD_00046359
Original NDA 213005 § 2.5	LIQ_PH-ILD_00045509
Original NDA 213005 § 2.6.1	LIQ_PH-ILD_00045498
Original NDA 213005 § 2.7.1	LIQ_PH-ILD_00045396
Original NDA 213005 § 3.2.P.4.6	LIQ_PH-ILD_00062236
Original NDA Cover Letter	LIQ_PH-ILD_00045978
Pre-IND meeting	LIQ_PH-ILD_00046114
Pre-NDA meeting	LIQ_PH-ILD_00046156
Pre-sNDA Meeting Request	LIQ_PH-ILD_00134026
Product Dossier	LIQ_PH-ILD_00146984
Schundler Press Release	LIQ_PH-ILD_00133247
U.S. Food & Drug Admin., Determining Whether to Submit an ANDA or a 505(b)(2) Application: Guidance for Industry (2019)	UTC_PH-ILD_227401
U.S. Food & Drug Admin., Guidance for Industry: Applications Covered by Section 505(b)(2): Draft Guidance (1999)	UTC_PH-ILD_227310

U.S. Food & Drug Admin., Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations: Draft Guidance (2014)	UTC_PH-ILD_227325
U.S. Food & Drug Admin., Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (2006)	UTC_PH-ILD_227354
U.S. Food & Drug Admin., Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (2013)	UTC_PH-ILD_227418
Weidman Email re: Pre-sNDA Meeting	LIQ_PH-ILD_00148509
Yutrepia Draft Webpage 2	LIQ_PH-ILD_00146936
Yutrepia Formulary Kit	LIQ_PH-ILD_00146970
Yutrepia Label	LIQ_PH-ILD_00126017
Yutrepia Marketing Diagram	LIQ_PH-ILD_00147156
Yutrepia Marketing Handout	LIQ_PH-ILD_00147141
Yutrepia PH-ILD sNDA	LIQ_PH-ILD_00091023
Yutrepia Presentation	LIQ_PH-ILD_00147196
	LIQ_PH-ILD_00130687
	LIQ_PH-ILD_00130689
	LIQ_PH-ILD_00148510
	UTC_PH-ILD_010670
	UTC_PH-ILD_048704
	LIQ_PH-ILD_00119653
	LIQ_PH-ILD_00141701
	LIQ_PH-ILD_00002010
	LIQ_PH-ILD_00045361
	LIQ_PH-ILD_00045335
	LIQ_PH-ILD_00045455
	LIQ_PH-ILD_00045454

# EXHIBIT 3



IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS  
CORPORATION,

Plaintiff,

v.

LIQUIDIA TECHNOLOGIES, INC.,

Defendant.

C.A. No. 1:23-cv-00975-RGA

**HIGHLY CONFIDENTIAL**

**REBUTTAL EXPERT REPORT OF BRADLEY M. WERTHEIM, M.D.**

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## **I. INTRODUCTION**

### **A. Scope of Analysis**

1. I, Bradley Wertheim, M.D., have been retained by counsel for Plaintiff United Therapeutics Corporation (“UTC” or “Plaintiff”) to provide my opinions regarding certain issues relating to the validity of certain claims of the ’327 patent. Specifically, UTC has asked me to analyze: (1) whether claims 1, 2, 6-11, and 14-16 of the ’327 patent are entitled to claim priority to the ’810 Provisional Application, filed on April 17, 2020; and (2) whether the as-issued specification of the ’327 patent provides sufficient written description support for claims 9 and 10.

2. I understand that in the above-captioned litigation, UTC asserts that Defendant Liquidia Technologies, Inc. (“Liquidia” or “Defendant”) has infringed of claims 1-11 and 14-19 of the ’327 patent (“Asserted Claims”) by seeking FDA approval to market Yutrepia (inhaled treprostinil) for the treatment of pulmonary hypertension associated with interstitial lung disease (“PH-ILD”). I understand that Liquidia contends that it does not infringe any Asserted Claim and that each of the Asserted Claims is invalid and/or unenforceable. Finally, I understand that the parties dispute whether the Asserted Claims are entitled to claim priority to the ’810 Provisional Application.<sup>1</sup>

3. As part of my analysis, UTC has also asked me to analyze and respond to certain opinions offered by Dr. Richard Channick on behalf of Liquidia in the Expert Report of Dr. Richard Channick, dated December 20, 2024. More Specifically, I have been asked to review Dr. Channick’s opinions that: (1) claims 1, 2, 6-11, and 14-16 of the ’327 patent are not entitled to a

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<sup>1</sup> UTC has not asked me to assess the priority date of claims 3-5, 12, 13, and 17-19 of the ’327 patent, and I offer no opinions in this regard below.

priority date of April 17, 2020; and (2) claims 9 and 10 of the '327 patent are invalid for lack of written description.<sup>2,3</sup>

**B. Summary of Opinions**

4. As discussed in more detail below, it is my opinion that:

- Claims 1, 2, 6-11, and 14-16 of the '327 patent are entitled to a priority date of April 17, 2020, which corresponds to the filing date of the '810 Provisional Application.
- Claims 9 and 10 of the '327 patent are supported by adequate written description in the specification.

**C. Qualifications**

5. I am an associate pulmonary and critical care physician and member of the Pulmonary Vascular Disease Program at Brigham and Women's Hospital in Boston, Massachusetts, where I serve as the Director of the Rheumatic Pulmonary Vascular Disease Clinic, a clinical program responsible for early diagnosis and management of pulmonary hypertension in patients with connective tissue diseases. I am also a pulmonary and critical care physician for the Veterans Affairs (VA) Boston Healthcare System in Boston, Massachusetts, where I serve as the Co-Director for the Pulmonary Vascular Disease Section. In this capacity, I am responsible for coordinating pulmonary hypertension care for veterans residing in Connecticut, Massachusetts, Vermont, New Hampshire, Rhode Island, and Maine, as well as those veterans in the eastern third

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<sup>2</sup> See generally Channick Op. Rpt. at ¶¶ 71-93, 425-436.

<sup>3</sup> I understand that Dr. Channick has also opined in his Opening Report that each of the Asserted Claims is invalid as anticipated and/or obvious over the relevant prior art. See, e.g., Channick Op. Rpt. at ¶¶ 94-424. UTC has not asked me to analyze the validity of any Asserted Claim with respect to anticipation and/or obviousness. However, as part of my priority analysis, UTC has asked me to review Dr. Channick's opinions regarding how a person of ordinary skill in the art ("POSA") would understand the disclosures of the prior art and what conclusions a POSA might be able to draw from those disclosures. To the extent I disagree with how Dr. Channick has interpreted a particular prior art reference, that disagreement is explained below.

of the United States seeking lung transplantation in the VA system. I specialize in treating patients with pulmonary vascular diseases, including all forms of pulmonary hypertension, such as pulmonary arterial hypertension (“PAH”), pulmonary hypertension associated with interstitial lung disease (PH-ILD), and other conditions leading to abnormal heart-lung interactions. In patients who have interstitial lung disease associated with their pulmonary hypertension (PH-ILD) or as a comorbidity of their non-PH-ILD forms of pulmonary hypertension, I serve as the treating pulmonologist for their interstitial lung disease (ILD). Accordingly, I am experienced in the treatment of ILD, including the use of immunomodulatory and antifibrotic medications, and acute exacerbations of ILD, which are discussed in detail in forthcoming sections. I have been practicing as an attending pulmonary and critical care physician since 2017. I have treated hundreds of inpatients and outpatients with advanced pulmonary vascular diseases and hundreds of patients with ILD. Further, I have been board certified in Internal Medicine, Pulmonary Disease, and Critical Care Medicine since 2014, 2016, and 2017, respectively.

6. I am an Assistant Professor of Medicine at Harvard Medical School in Boston, Massachusetts. I teach or have taught post-doctoral courses relating to, for example, pulmonary hypertension, cardiovascular medicine, and advanced pulmonary hypertension management. I have also taught continuing education courses for peers on topics relating to pulmonary vascular disease. Moreover, I have been invited over 40 times to present on topics relating to diseases and treatment interventions for pulmonary vascular diseases by local, regional, national, and international entities.

7. I received my Bachelor of Science degree in Biochemistry from Lafayette College in Easton, Pennsylvania in 2007. I received my Doctor of Medicine (MD) degree from Harvard Medical School in Boston, Massachusetts in 2011. I completed my internship as well as my

residency in Internal Medicine at Massachusetts General Hospital in Boston, Massachusetts in 2012 and 2014, respectively. I completed a clinical fellowship in Pulmonary and Critical Care Medicine at Brigham and Women's Hospital in Boston, Massachusetts in 2017. During this time, I was the first physician selected for the Burke Advanced Fellowship in Pulmonary Heart Disease at Brigham and Women's Hospital in Boston, Massachusetts, which was one of the first formal pulmonary hypertension training programs in the United States. Lastly, I completed a post-doctoral research fellowship in network science and pulmonary vascular biology at Brigham and Women's Hospital in 2019.

8. I have authored or co-authored roughly 40 peer-reviewed publications, book chapters, commentaries, other scientific or medical publications, reports, abstracts, and poster presentations. My primary research interests include understanding the biology, mechanisms, and propagation of vascular fibrosis and identifying novel treatment strategies for pulmonary circulation diseases. My book chapter on Systems Pharmacology (in Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 5<sup>th</sup> edition, in press) is scheduled for use by medical students in the first-year clinical pharmacology course at Harvard Medical School. I also serve as an ad hoc reviewer for 16 peer-reviewed journals such as American Journal of Respiratory and Critical Care Medicine, Annals of the American Thoracic Society, Chest, Journal of Heart and Lung Transplantation, Journal of the American College of Cardiology, and Scientific Reports. As an investigator, I run a research laboratory that is funded by the National Heart Lung and Blood Institute / National Institutes of Health to study pulmonary vascular biology and mechanisms of pulmonary hypertension. I have specific expertise in studying biological mechanisms of inflammation and fibrosis in lung conditions.

9. I am qualified based on my education and professional experience to provide expert testimony in this matter. My education and training qualify me as at least a person of ordinary of skill in the art at the time of invention in 2020. While the paragraphs above summarize my experience and qualifications, a more detailed listing of my professional experience is described in my curriculum vitae, which is attached as **Exhibit 1**.

**D. Materials Considered**

10. Unless otherwise stated, in forming and rendering the opinions and analysis in this report, I have reviewed, among other things, the materials cited in this report and those referenced in the above-listed Materials Considered & Table of Abbreviations,<sup>4</sup> in addition to the Channick Report and the materials cited therein. I have also relied on my background and experience, which is summarized in Section I.C. as well as in my *curriculum vitae* (attached as **Exhibit 1**). To the extent not identified in my list of Materials Considered, I have also considered each of the documents or materials cited in this report. To the extent I have only cited or referred to a portion of a particular document below, I reserve the right to rely on the document in its entirety in future reports and/or in my forthcoming trial testimony.

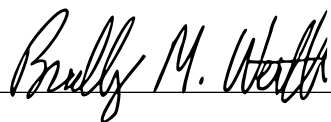
**E. Compensation**

11. I am being compensated for my time spent working on this matter at my standard consulting rate of \$750.00 per hour, plus reasonable expenses. I have no other interest in this litigation or in any party to this litigation. My compensation does not depend on my performance, the substance of my analysis or opinions, the outcome of this case, or any issues involved in or related to this case.

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<sup>4</sup> *Supra*, pp. v-xvii.

I declare under penalty of perjury that the foregoing is true and correct to the best of  
my knowledge. Executed on Jan. 23, 2025 at Boston, Mass.

A handwritten signature in black ink, reading "Bradley M. Wertheim", is written over a horizontal line.

Bradley M. Wertheim, M.D.

**EXHIBIT 1**

## Harvard Medical School Curriculum Vitae

**Date Prepared:** December 30, 2024

**Name:** Bradley M. Wertheim, M.D.

**Office Address:** Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, 15 Francis Street, Boston, MA 02115

**Work Phone:** 617-732-7420

**Work Email:** bwertheim@bwh.harvard.edu

**Work FAX:** 617-732-7421

### Education

2007	BS ( <i>summa cum laude</i> )	Biochemistry	Lafayette College, Easton, PA
2011	MD	Medicine	Harvard Medical School (HMS), Boston, MA

### Postdoctoral Training

6/11-6/14	Intern/Resident	Internal Medicine	Massachusetts General Hospital (MGH), Boston, MA
6/11-6/14	Clinical Fellow	Medicine	HMS
7/14-6/17	Clinical Fellow	Pulmonary and Critical Care Medicine	Brigham and Women's Hospital (BWH), Boston, MA
7/14-6/19	Research Fellow	Medicine (Bradley Maron, MD; Joseph Loscalzo MD, PhD)	BWH
7/15-6/16	Fellow	Burke Advanced Fellowship in Pulmonary Heart Disease	BWH

### Faculty Academic Appointments

7/19-3/2024	Instructor	Medicine	HMS
3/24-	Assistant Professor	Medicine	HMS

### Appointments at Hospitals/Affiliated Institutions

11/16-	Intensivist	Medicine	Newton Wellesley Hospital, Newton, MA
7/17-	Associate Physician	Pulmonary and Critical Care Medicine	BWH
9/23-	Physician	Pulmonary and Critical Care Medicine	VA Boston Healthcare System, Boston, MA

### Other Professional Positions

2017	Consultant, Excellence On-Demand Education Curriculum	Cornell School of Hotel Administration Service (Unpaid)
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2020-2022 Medical Consultant Change Healthcare, Newton, MA

### **Major Administrative Leadership Positions**

#### **Local**

2023- Co-Director, Pulmonary Vascular Disease Section VA Boston, Healthcare System, Boston MA

### **Committee Service**

#### **Local**

2007–2011	Student Government Financial Aid	HMS Representative
2011-2014	Laboratory Utilization Committee	MGH Member
2011-2014	Internal Medicine Resident Quality and Safety Committee	MGH  Member
2012	Accreditation Council for Graduate Medical Education Site Visit	MGH
2016	2012 Medical Intensive Care Unit (MICU) Phenobarbital Protocol for Complicated Alcohol Withdrawal Project	Member (voted by peers) W. Roxbury VA Medical Center
2016-2017	BWH MICU Vascular Access Cart Project	Member BWH Physician Co-Leader
2017	Accreditation Council for Graduate Medical Education Site Visit	Pulmonary and Critical Care Medicine, BWH
2017	2017 Mass General Brigham (MGB) Center for COVID Innovation Healthcare Subcommittee	Member (voted by peers) MGB
2020-	Pulmonary and Critical Care Medicine T32 Advisory Committee	Member BWH
2023-	Pulmonary Embolism Response Team Advisory Committee	Member Newton-Wellesley Hospital
		Member

### **Professional Societies**

2011-2014	American College of Chest Physicians	Member
2017-	Pulmonary Vascular Research Institute	Member
2017-	American Thoracic Society	Member
2023-		Postgraduate Course in Right Heart Hemodynamics
2023-		Member, Pulmonary Circulation Programming Committee
2023-		Conference Co-Organizer, Pulmonary Circulation Committee
2019-	American Heart Association	Member, Junior International Scholars Network, Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation

2019- 2023-	Massachusetts Medical Society North American Thrombosis Forum	Member Conference Organizer, 6 <sup>th</sup> Biannual Right Heart Symposium. Selected to serve on the organizing committee for the 7 <sup>th</sup> Symposium scheduled for 2025.
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### **Editorial Activities**

#### ***Ad hoc Reviewer***

*American Journal of Medicine*  
*American Journal of Respiratory and Critical Care Medicine*  
*Annals of the American Thoracic Society*  
*Chest*  
*Circulation: Cardiovascular Imaging*  
*Circulation: Heart Failure*  
*Clinical Cardiology*  
*European Respiratory Journal Open*  
*Journal of Heart and Lung Transplantation*  
*Journal of Hospital Medicine*  
*Journal of the American College of Cardiology*  
*Journal of the American College of Cardiology: Case Reports*  
*Journal of the American Heart Association*  
*New England Journal of Medicine Healer (NEJM video game)*  
*Respiratory Research*  
*Scientific Reports*

### **Honors and Prizes**

2003-2007	Trustee Scholarship	Lafayette College	
2004-2006	Excel Scholarship	Lafayette College	
2006	Sigma Xi	Lafayette College, Scientific Research Honor Society	Research
2007	Phi Lambda Upsilon	Lafayette College, Chemistry Honor Society	Academic
2007	Merck Index Award	Lafayette College	
2008-2010	Howard G. Lapsley Memorial Scholarship	Muhlenberg Foundation	
2017	Basic Science Fellowship Award	Pulmonary Vascular Disease Research Institute	Research
2018-2020	Selected for Divisional T32 Training Award (HL007633)	Division of Pulmonary and Critical Care Medicine, BWH	Research
2019	Hearst Young Investigator Award	BWH & Hearst Foundation	Research
2023	Core Laboratory Voucher Award	Department of Medicine, BWH	Research

### **Report of Funded and Unfunded Projects**

#### **Funding Information**

##### **Past**

2017-2020	Mechanisms of Disease Inception in Pulmonary Arterial Hypertension Pulmonary Vascular Research Institute Principal Investigator (PI)
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This project focused on characterizing the pathobiology of early pulmonary vascular fibrosis and identifying novel therapeutic targets specific to PAH disease inception.

2020-2021 Proline Bioavailability, Endothelial Fibrosis, and Early Pulmonary Arterial Hypertension  
BWH Hearst Young Investigator Award  
PI

This project aimed to understand how interaction between C-terminal src kinase (Csk) and delta-1-pyrroline-5-carboxylate synthase (P5CS) controls pathogenic endothelial collagen synthesis in early-stage pulmonary arterial hypertension.

## Current

2020-2025 Ubiquitination and Endothelial Fibrosis in Early Pulmonary Arterial Hypertension  
National Institutes of Health (NIH)/National Heart, Lung and Blood Institute (NHLBI)  
5K08HL151976-02  
PI (\$785,000)

This project proposes to investigate the role of redox-regulated endothelial C-terminal src kinase as a mediator of vascular fibrosis in early-stage pulmonary arterial hypertension (PAH).

2024-2026 Endothelial Proline Utilization in Pulmonary Arterial Hypertension  
NIH/NHLBI R03  
PI – Direct Costs Requested - \$150,000

This grant aims to build on the observations we made in our 2023 *JCI Insight* paper that pulmonary arterial hypertension (PAH) is associated with increased avidity of the amino acid proline in pulmonary endothelial and medial cell types. We propose to 1) Establish Csk-Src regulation of HPAEC proline availability and fibroproliferative biomass *in vitro* and 2) Establish Csk-Src dependent proline dysregulation in experimental early-stage PAH and human PAH *in vivo*.

## Projects Submitted for Funding

Submitted 2/2/2024 Endothelial Inflammation, Src Kinase Dysregulation, and Fibrosis in Early Pulmonary Arterial Hypertension  
NIH/NHLBI R01  
PI – Direct Costs Requested - \$2,625,250  
The central goal of this proposal is to identify the molecular mechanism regulating Csk dysfunction in early-stage pulmonary arterial hypertension and the functional consequences of this mechanism for pathologic collagen 22 synthesis in pulmonary arterioles. We propose to 1) Test the hypothesis that inflammation promotes Csk dysfunction and Src activation in HPAECs and 2) Define the pulmonary vascular phenotype of Csk-dependent collagen 22. Understanding Csk-Src dependent Col22A1 vasculopathy may identify strategies to target the inception of pulmonary vascular remodeling, which may have implications for PAH prevention in high-risk connective tissue disease patients.  
Scientific Review Group Action: Impact/Priority Score: 33

## Report of Local Teaching and Training

### Teaching of Students in Courses

#### HMS/HSDM/DMS Courses

2015-2016	Human Systems: Respiratory Pathophysiology (IN757.RES)	HMS
	Medical Students	5 hrs/week for 2.5 weeks

2016	Patient Doctor II Pulmonary Examination Medical Students (IN761)	HMS 3 hr session/yr
2016	Patient Doctor II Cardiovascular Examination Medical Students (IN761)	HMS 3 hr session/yr
2017-	The Practice of Medicine: Basic Pulmonary Examination Medical Students (POM100.23)	HMS 3 hr session/yr
2017-	The Practice of Medicine: Basic Cardiovascular Examination (POM100.23) Medical Students	HMS 3 hr session/yr
2018	Internal Medicine Bootcamp – Approaches to Shock and Central Line Training Medical Students	4 hr session/yr

**Formal Teaching of Residents, Clinical Fellows and Research Fellows (post-docs)**

2015	Perioperative Management of Pulmonary Hypertension Pulmonary and critical care medicine fellows	BWH 1 hr lecture
2016	ICU Management of Pulmonary Hypertension Surgical ICU residents and fellows	BWH 1 hr lecture
2019	Pulmonary Vascular Disease 1 <sup>st</sup> yr Pulmonary and critical care medicine fellows	BWH 1 hr lecture
2019 -	Introductory Course for Allergy and Immunology - Lung physiology, PFTs, and cases Allergy and Immunology clinical fellows	BWH 1 hr lecture x 4 yrs
2021, 2022, 2024	Introduction to Pulmonary Hypertension Pulmonary and critical care medicine fellows	BWH 1 hr lecture
2022-	Introduction to Pulmonary Hypertension Cardiovascular Medicine fellows	BWH 1 hr lecture
2023	Advanced Pulmonary Hypertension Management Pulmonary and critical care medicine fellows	BWH 1 hr lecture
2024	Pulmonary hypertension Internal medicine residents	BWH 1 hr lecture
2024	Pulmonary Hypertension Cardiovascular Fellows	BWH 1 hr lecture
2024	Pulmonary Hypertension Internal medicine residents	BWH 1 hr lecture
2024	Critical care approach to right heart failure Internal medicine residents	BWFH 1 hr lecture

**Clinical Supervisory and Training Responsibilities**

2017-	Substitute ambulatory preceptor PCCM Fellows	BWH – Lung Center 4 hrs/yr
2017-	Inpatient ICU Preceptor Internal Medicine Residents	Newton Wellesley Hospital 12-24 hrs/month
2019-	Inpatient Pulmonary Vascular Disease (PVD) Consults Preceptor	BWH 45 hrs/week, 6 weeks/yr

	Internal Medicine Interns, Residents, and PCCM Fellows	
2020	Inpatient COVID ICU preceptor Internal Medicine Interns, Residents, and PCCM Fellows	BWH 40 hrs/week, 2 weeks/yr (and as needed pending pandemic trajectory)
2020-2023	BWH Intern Physician Coaching Program: Career Advisor Internal Medicine House staff	BWH 8 hrs/year
2020-	Ambulatory Subspecialty Preceptor: PVD Clinic Internal Medicine Residents	BWH 5 hrs/session, 4 sessions/year
2020-	Bedside Procedural Service Internal Medicine Interns, Residents, Physician Assistant Fellows	BWH 35 hrs/week, 1 week/year
2021-	Ambulatory Subspecialty Preceptor: PVD Clinic Cardiovascular medicine fellows	BWH 5 hrs/session, 8 sessions/year
2023-	Ambulatory Subspecialty Preceptor: PVD Clinic Burke Fellow in Pulmonary Heart Disease	West Roxbury VA Hospital 3 hrs/session, 15 sessions/year

#### **Laboratory and Other Research Supervisory and Training Responsibilities**

2017-	Research supervision Staff scientist	Maron Laboratory, BWH 3 hrs/week yearly until 2023. 34 hrs/week yearly 2023-
2021-	Research supervision Research fellow	Division of Pulmonary and Critical Care Medicine, BWH 0.5 hr/month
2022-2024	Research supervision Internal medicine resident	Division of Pulmonary and Critical Care Medicine, BWH 2 hrs/week

#### **Mentored Trainees and Faculty**

2017-2019	Elena Arons, MD / Staff Scientist, Division of Cardiovascular Medicine, BWH <i>Career Stage:</i> Staff scientist. <i>Mentoring Role:</i> Co-mentor. <i>Accomplishments:</i> conducted research on endothelial cell isolation, characterization, and culture; co-authored publication.
2021-	Ann Marcia Tukpah, MD / Clinical, Pulmonary and Critical Care Medicine, BWH; Research Fellow in Medicine, HMS <i>Career Stage:</i> Fellow. <i>Mentoring Role:</i> Research advisor on T32 committee. <i>Accomplishments:</i> accepted to BWH PCCM T32, submitted NIH loan repayment program application.
2022-2024	Michael S. Miller, MD / Resident, Internal Medicine, BWH <i>Career Stage:</i> Resident. <i>Mentoring Role:</i> Research mentor. <i>Accomplishments:</i> research project studying the association of phosphodiesterase inhibition and esophageal dysmotility in pulmonary arterial hypertension and the implications for lung transplantation evaluation. Manuscript published 4/2024, M.S.M. as first-author, B.M.W. as senior-author.

#### **Formal Teaching of Peers (e.g., CME and other continuing education courses)**

*No presentations below were sponsored by outside entities*

2019	Central Venous Catheter Placement Bedside Procedure Service Faculty Simulation, BWH	4-hour session Boston, MA
2020	Pulmonary arterial hypertension: Clinical presentation, diagnosis, therapy, and prognosis The Brigham Board Review in Pulmonary – “Studio”/Distance Learning Course, BWH	1-hour audio recorded lecture Boston, MA

2020	Challenging Pulmonary Cases Brigham and Women's Intensive Review of Internal Medicine, BWH	30-minute lecture Boston, MA
2020	Asthma Evaluation and Testing The Brigham Board Review in Allergy and Immunology: Studio/Distance Learning	30-minute lecture Virtual
2020	Pulmonary Board Review 5 <sup>th</sup> Annual Update in Pulmonary and Critical Care Medicine	30-minute lecture Boston, MA
2022	Pulmonary arterial hypertension: Clinical presentation, diagnosis, therapy, and prognosis The Brigham Board Review in Pulmonary – "Studio"/Distance Learning Course, BWH	1-hour audio recorded lecture  Boston, MA

### **Local Invited Presentations**

*No presentations below were sponsored by outside entities*

2015	Exercise-induced pulmonary hypertension / case presentation Pulmonary Vascular Disease Conference, BWH
2015	Air in the wrong part of the lung / Pulmonary Grand Rounds Pulmonary and Critical Care Medicine Division, BWH
2015	A legendary case of respiratory failure (from 1952) / Pulmonary Grand Rounds Pulmonary and Critical Care Medicine, BWH
2015	Case Presentation: Exercise-induced pulmonary hypertension / invited lecture Bornstein Cardiology Conference, BWH
2016	Extracorporeal life support for massive pulmonary embolism: case presentation and review of the literature / invited lecture Pulmonary Vascular Disease Conference, BWH
2016	Extracorporeal life support for massive pulmonary embolism: case presentation and review of the literature / invited lecture Bornstein Cardiology Conference, BWH
2017	Reverse-engineering pulmonary vascular disease: insights from borderline pulmonary arterial hypertension / invited lecture Pulmonary Vascular Disease Conference, BWH
2017	Pulmonary function testing for the thoracic radiologist / invited lecture Radiology Resident Teaching Conference, BWH
2017	Mechanisms of disease inception in pulmonary arterial hypertension / invited talk Pulmonary Vascular Disease Conference, BWH
2018	Mechanisms of disease inception in pulmonary arterial hypertension / invited talk Work-in-Progress, Pulmonary and Critical Care Medicine, BWH
2019	Mechanisms of disease inception in pulmonary arterial hypertension / invited talk Pulmonary and Critical Care Medicine, Work-in-Progress, BWH
2019	Pulmonary function testing / Allergy Grand Rounds MGH, Boston, MA
2019	Pulmonary hypertension in connective tissue disease: Managing the spectrum of clinical risk / Rheumatology Grand Rounds Rheumatology Division, BWH
2019	Pulmonary hypertension for the bedside nurse / invited talk Shapiro Cardiovascular Center, BWH
2020	Endothelial fibrosis in early-stage pulmonary arterial hypertension / invited presentation Work-in-Progress Conference, Pulmonary and Critical Care Medicine, BWH
2020	Pulmonary hypertension management / panel discussant Department of Medicine, W. Roxbury VA Medical Center, Boston, MA

2020	Pulmonary function testing: Indications and interpretation / Allergy Grand Rounds Teleconference, Pulmonary Division, MGH (virtual)
2020-2024	Pulmonary hypertension for the bedside nurse / invited talk (x 7) Shapiro Cardiovascular Center, BWH (virtual)
2020	Cardiovascular Life Sciences Research Series / invited presentation BWH (virtual)
2022	Bad tracheostomies / panelist – Laryngology Grand Rounds Mass Eye and Ear Institute, Boston, MA
2022, 2024	Pulmonary function testing / Allergy Grand Rounds MGH, Boston, MA
2022	Connective tissue disease associated pulmonary hypertension / Rheumatology Grand Rounds Department of Medicine, BWH (virtual)
2022	Proline and glucose metabolic reprogramming support vascular endothelial and medial biomass in pulmonary arterial hypertension / Invited talk MGB Department of Medicine Research Seminar Series MGH and BWH (virtual)
2023	Proline and glucose metabolic reprogramming support vascular endothelial and medial biomass in pulmonary arterial hypertension / Invited talk Cardiovascular Life Sciences Research Series, BWH
2023	Pulmonary endothelial inflammation dysregulates src family kinase signaling to increase collagen 22 prior to the development of severe pulmonary hypertension / Invited talk Work-in-Progress Research Seminar Series, Division of Pulmonary and Critical Care Medicine, BWH
2024	Management of Right Heart Failure / Invited talk 11C ICU Lecture Series, BWH
2024	Pulmonary hypertension and RV failure / Invited talk Vascular Medicine Conference series, Division of Cardiovascular Medicine, BWH
2024	Cardiovascular Work-in-Progress Conference / Invited moderator MGH, BWH, Broad Institute, Boston MA
2024	Inflammation disrupts Csk activity to promote Src activation and fibrosis in early-stage pulmonary arterial hypertension / Invited talk Work-in-Progress Research Seminar Series, Division of Pulmonary and Critical Care Medicine, BWH

**Report of Regional, National and International Invited Teaching and Presentations**  
**Invited Presentations and Courses**

*No presentations below were sponsored by outside entities*

**Regional**

2015	A 51-year-old woman with cough / invited talk Intracity Pulmonary Conference, Boston University, Boston, MA
2024	A Practical Approach to Pulmonary Hypertension Medicine Grand Rounds, Veterans Affairs Boston Healthcare System, Boston, MA

**National**

2019	The Role of Invasive Exercise Testing for Diagnosis and Treatment of Right Heart Failure / Invited lecture Case-Based Clinical Management of Patients with Right Heart Failure, American Heart Association Scientific Sessions, Philadelphia, PA
2019	Update in CTEPH: From Bench to Bedside / Invited moderator American Heart Association Scientific Session, Philadelphia, PA

- 2020 Current and Emerging Strategies to Manage RV Shock in the Setting of RV Infarct / Invited lecture  
Critical Clinical Conundrums in Acute Coronary Syndromes / Invited lecture  
American College of Cardiology Annual Scientific Sessions, Chicago, IL  
*This presentation was scheduled, but then cancelled because of a Covid-19 travel/meeting ban*
- 2020 Pulmonary Hypertension Clinical Trials with Novel Approaches / Invited Social Media Moderator  
American Heart Association Scientific Sessions, Dallas, TX  
*This presentation was scheduled, but then cancelled because of a Covid-19 travel/meeting ban*
- 2021 Submassive pulmonary embolism / Invited moderator  
North American Thrombosis Forum 5<sup>th</sup> Right Heart Symposium, Boston, MA
- 2022 Where We Are Today: Beyond the Original Description of Pulmonary Arterial Hypertension / Invited lecture  
American College of Cardiology Annual Scientific Session, Washington, DC
- 2022 Controversies in RV dysfunction and management: A pro-con debate / Invited moderator  
American Heart Association Scientific Session, Chicago, IL
- 2022 Vascular fibrosis in early-stage pulmonary arterial hypertension / invited lecture  
Pulmonary and Critical Care Medicine Lung Research Conference, Johns Hopkins Hospital, Baltimore, MD
- 2023 RV: the “other” ventricle / Invited moderator  
Technology and Heart Failure Therapeutics 2023 Meeting, Boston MA
- 2023 Don't Forget about the Blood Vessels! Pulmonary Vascular Function in Acute Lung Injury / Invited Moderator, American Thoracic Society 2023 Meeting, Washington DC
- 2023 Clinical Pearls and Emerging Insights into CTEPH Biology and Treatment / Invited Moderator, American Heart Association Scientific Sessions

### **International**

- 2022 Clinical Tutorials in Pulmonary Arterial Hypertension / Invited moderator  
Management of pericardial effusion in PAH: Don't tap, fact or fiction / Invited Moderator  
15<sup>th</sup> Annual World Congress on Pulmonary Vascular Disease, Pulmonary Vascular Research Institute, Athens, Greece  
Pulmonary Vascular Research Institute World Congress, Athens, Greece
- 2022 An update on clinical trials in PAH / Invited moderator  
Pulmonary Vascular Research Institute World Congress, Athens, Greece
- 2023 Vasopressor Support in Right Heart Failure: Can We Optimize RV Mechanics and Coronary Perfusion?  
6<sup>th</sup> Biannual Right Heart Symposium, North American Thrombosis Forum, Boston, MA
- 2024 The Next 50 Years of Pulmonary Hypertension: A Global View/  
Invited Moderator, Pulmonary Vascular Research Institute World Congress
- 2024 Are Mitochondria the Instigator of Pulmonary Arterial Hypertension?  
Invited Moderator, Pulmonary Vascular Research Institute Digital Webinar
- 2024 Critical Care Management of the Patient With Advanced Pulmonary Hypertension and Shock Who Develops Right Ventricular Ischemia  
Invited speaker, Right Heart Mini Symposium, North American Thrombosis Forum, Boston, MA

### **Report of Clinical Activities and Innovations**

#### **Current Licensure and Certification**

- 2014 Massachusetts Medical License

2014 American Board of Internal Medicine (ABIM)  
 2016 ABIM – Pulmonary Disease  
 2017 ABIM – Critical Care Medicine

### **Practice Activities**

2017-2018	Ambulatory	General Pulmonary Clinic, BWH	½ session every other week
2017-	Inpatient	Intensivist / Newton Wellesley Hospital	1-2 per diem shifts/month
2018-	Ambulatory	Pulmonary Vascular Disease Clinic, BWH	½ session every other week
2018-2019	Inpatient	Pulmonary Vascular Disease Service, BWH	2 weeks/yr
2019-	Inpatient	Pulmonary Vascular Disease Service, BWH	6 weeks/yr
2020	Inpatient	COVID-19 Special Pathogen ICU and MICU Overflow Attending BWH	2 weeks/year and as needed during COVID pandemic
2020	Virtual Care	Indian Health Services Critical Care Consult Pager Coverage	2 weeks/year and as needed during COVID pandemic
2020-	Inpatient	Bedside Procedure Service, BWH	2 weeks/yr
			2023- PRN coverage

### **Clinical Innovations**

Rheumatic Pulmonary Vascular Disease Clinic (RPVD) Clinic (2019-)

Connective tissue disease associated pulmonary hypertension (PH) is associated with increased morbidity and mortality compared to other forms of pulmonary hypertension—especially for patients with systemic sclerosis (scleroderma). Reasons for this include delayed diagnosis and frequent co-occurrence of PH with conditions such as interstitial lung disease, left-sided heart disease, and pulmonary venous remodeling. A collaboration with Dr. Paul Dellaripa of the BWH Division of Rheumatology, Inflammation, and Immunity, the goal of the RPVD is to improve clinical PH outcomes in this vulnerable population through systematic screening, timely consultation, multidisciplinary risk-assessment, early treatment, and a platform for translational research.

### **Technological and Other Scientific Innovations**

Provisional US patent coversheet application no. 63/541,939, “Methods and Materials in Pulmonary Arterial Hypertension.” (2023)

Co-inventor on a novel adenovirus-based therapeutic strategy to inhibit vascular fibrosis and endothelial cell dysfunction. Provisional US patent application filed by Mass General Brigham 10/2/2023.

### **Report of Education of Patients and Service to the Community**

#### **Educational Material for Patients and the Lay Community**

*No educational materials below were sponsored by outside entities*

#### **Books, monographs, articles and presentations in other media**

2011 The Doctor Can't See You Now Author *Los Angeles Times*, January 24, 2011

2013	How Not to Die of Botulism	Author	<a href="https://www.latimes.com/archives/la-xpm-2011-jan-24-la-oe-wertheim-mdshortage-20110124-story.html">https://www.latimes.com/archives/la-xpm-2011-jan-24-la-oe-wertheim-mdshortage-20110124-story.html</a> <i>The Atlantic</i> , December 2, 2013 <a href="http://www.theatlantic.com/health/archive/2013/12/how-not-to-die-of-botulism/281649/">http://www.theatlantic.com/health/archive/2013/12/how-not-to-die-of-botulism/281649/</a>
2013	The Iron in Our Blood That Keeps and Kills Us	Author	<i>The Atlantic</i> , January 10, 2013 <a href="http://www.theatlantic.com/health/archive/2013/01/the-iron-in-our-blood-that-keeps-and-kills-us/266936/">http://www.theatlantic.com/health/archive/2013/01/the-iron-in-our-blood-that-keeps-and-kills-us/266936/</a>
2020	How a Polio Outbreak in Copenhagen Led to the Invention of the Ventilator	Author	<i>Smithsonian Magazine</i> , June 10, 2020 <a href="https://www.smithsonianmag.com/innovation/how-polio-outbreak-copenhagen-led-to-invention-ventilator-180975045/">https://www.smithsonianmag.com/innovation/how-polio-outbreak-copenhagen-led-to-invention-ventilator-180975045/</a>

### **Recognition**

2020	Interviewee / Bio Quest, History of Pandemics: Part 1	Doordarshan News (India's largest public broadcaster) <a href="https://www.youtube.com/watch?v=C-82e3CA9rU">https://www.youtube.com/watch?v=C-82e3CA9rU</a>
2021	Interviewee / Virus (forthcoming documentary)	Amos Pictures, HBO/BBC-affiliated project
2021	Interviewee/When Tuberculosis Patients Quarantined Inside Kentucky's Mammoth Cave	<i>Smithsonian Magazine</i> <a href="https://www.smithsonianmag.com/travel/when-tuberculosis-patients-quarantined-inside-kentuckys-mammoth-cave-180978144/">https://www.smithsonianmag.com/travel/when-tuberculosis-patients-quarantined-inside-kentuckys-mammoth-cave-180978144/</a>
2023-	Selected for Top Doctors List, Pulmonology	Castle Connolly
2024	Selected for Top Doctors List, Pulmonology	Boston Magazine

### **Report of Scholarship**

<http://orcid.org/0000-0002-1414-4692>

### **Peer reviewed publications in print or other media**

#### **Research Investigations**

1. Sokolowsky K, Newton M, Lucero C, **Wertheim B**, Freedman J, Cortazar F, Czochor J, Schelvis JP, Gindt YM. Spectroscopic and thermodynamic comparisons of escherichia coli DNA photolyase and vibrio cholera cryptochrome 1. *J Phys Chem B*. 2010;114(20):7121-30. PMID: 20438097.
2. Banagan BL, **Wertheim BM**, Roth MJ, Caslake LF. Microbial strengthening of loose sand. *Lett Appl Microbiol*. 2010;51(2):138-42. PMID: 20557452.
3. Rudolf JW, Dighe AS, Coley CM, Kamis IK, **Wertheim BM**, Wright DE, Lewandrowski KB, Baron JM. Analysis of daily laboratory orders at a large urban academic center: A multifaceted approach to changing test ordering patterns. *Am J Clin Pathol*. 2017;148(2):128-35. PMID: 28898984; PMCID: PMC6322419.
4. Opatowsky AR, Hess E, Maron BA, Brittain EL, Barón AE, Maddox TM, Alshawabkeh LI, **Wertheim BM**, Xu M, Assad TR, Rich JD, Choudhary G, Tedford RJ. Thermolulution vs estimated Fick cardiac output measurement in clinical practice: An analysis of mortality from the Veterans Affairs Clinical Assessment, Reporting, and Tracking (VA CART) program and Vanderbilt University. *JAMA Cardiol*. 2017;2(10):1090-9. PMID: 28877293; PMCID: PMC5710449.
5. **Wertheim BM**, Aguirre AJ, Bhattacharyya RP, Chorba J, Jadhav AP, Kerry VB, Macklin EA, Motyckova G, Raju S, Lewandrowski K, Hunt DP, Wright DE. An educational and administrative

intervention to promote rational laboratory test ordering on an academic general medicine service. *Am J Med.* 2017;130(1):47-53. PMID: 27619354; PMCID: PMC6598201.

6. Oldham WM, Oliveira RKF, Wang RS, Opatowsky AR, Rubins DM, Hainer J, **Wertheim BM**, Alba GA, Choudhary G, Torniyos A, MacRae CA, Loscalzo J, Leopold JA, Waxman AB, Olschewski H, Kovacs G, Systrom DM, Maron BA. Network analysis to risk stratify patients with exercise intolerance. *Circ Res.* 2018;122(6):864-76. PMID: 29437835; PMCID: PMC5924425.
7. Samokhin AO, Stephens T, **Wertheim BM**, Wang RS, Vargas SO, Yung LM, Cao M, Brown M, Arons E, Dieffenbach PB, Fewell JG, Matar M, Bowman FP, Haley KJ, Alba GA, Marino SM, Kumar R, Rosas IO, Waxman AB, Oldham WM, Khanna D, Graham BB, Seo S, Gladyshev VN, Yu PB, Fredenburgh LE, Loscalzo J, Leopold JA, Maron BA. NEDD9 targets COL3A1 to promote endothelial fibrosis and pulmonary arterial hypertension. *Sci Transl Med.* 2018;10(445): eaap7294. PMID: 29899023; PMCID: PMC6223025.
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**Wertheim BM**, Wang, R, Zhang Y, Samokhin AO, Alba GA, Arons E, Oldham WM, Maron BA. C-terminal src kinases inhibits endothelial fibrosis and is upregulated in early-stage experimental pulmonary arterial hypertension. Endothelial Function and Pulmonary Vascular Remodeling. American Heart Association Scientific Sessions; 2021 November 13; Boston, Massachusetts, United States (virtual).

**Wertheim BM**, Wang, R, Zhang Y, Samokhin AO, Alba GA, Arons E, Oldham WM, Maron BA. C-terminal src kinases inhibits endothelial fibrosis and is upregulated in early-stage experimental pulmonary arterial hypertension. Alan Lerner Research Symposium, Brigham and Women's Hospital; 2021 August 12; Boston, Massachusetts, United States (virtual).

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# EXHIBIT 4



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IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS  
CORPORATION,

Plaintiff,

vs. C.A. NO. 23-975-RGA-SRF

LIQUIDIA TECHNOLOGIES, INC.,

Defendants.

HIGHLY CONFIDENTIAL  
VIDEO-RECORDED DEPOSITION  
OF RONALD A. THISTED, Ph.D.

March 14, 2025

Sage Boardroom, Four Seasons Resort Rancho Encantado  
198 State Road 592  
Santa Fe, New Mexico 87506

9:35 a.m.

PURSUANT TO THE DELAWARE RULES OF CIVIL  
PROCEDURE, this deposition was:

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1 Q. When you were preparing your reply report  
2 did you speak with Drs. Nathan or Wertheim?

3 A. No, I did not.

4 Q. At any time have you ever spoken with  
5 Dr. Nathan about the subject matter of this case?

6 A. No, I have not.

7 Q. Have you ever spoken with Dr. Wertheim  
8 about this case?

9 A. No.

10 Q. It is safe to say, then, that the opinions  
11 you are offering in this case don't rely on any  
12 conversations you have had with Dr. Nathan or  
13 Dr. Wertheim?

14 A. They don't rely on conversations with  
15 those individuals.

16 Q. When were you first retained as an expert  
17 in this case?

18 A. I believe I was first retained in the fall  
19 of 2024.

20 Q. Okay. Do you recall what month?

21 A. I believe it was September or October.

22 Q. How did it come to pass that you were  
23 retained as an expert in this case?

24 MR. BURROWBRIDGE: Objection, form.

25 A. I was originally contacted, I believe, in

1 skill in the art, which I will call a POSA for the  
2 rest of the day, P-O-S-A.

3 A. Yes.

4 Q. For purposes of the '327 patent you have  
5 UTC's position and Liquidia's position in a box on  
6 Page 9.

7 Do you see that?

8 A. I do.

9 Q. You do not personally qualify as a POSA  
10 under UTC's definition, correct?

11 A. Although I don't have a medical degree and  
12 I don't treat PH-ILD patients, I have expertise that  
13 overlaps with what a POSA would have as relates to  
14 issues such as biostatistics, study design, analysis  
15 of studies, and evaluation of what they do and do  
16 not say, which would be part of -- which would be  
17 within the scope of what a POSA would have to have  
18 in order to review these patents.

19 Q. You do not have an MD, correct?

20 A. I do not.

21 Q. You do not have any experience treating  
22 patients with interstitial lung disease, correct?

23 A. That's correct.

24 Q. Let alone patients with PH-ILD?

25 A. Correct.

1 Q. Therefore you do not have the level of  
2 experience that is specified in UTC's definition of  
3 a POSA, correct?

4 MR. BURROWBRIDGE: Objection, form.

5 A. Again, while I do not have all the -- all  
6 of the components of what this definition of a POSA  
7 would entail, I do have some components of what I  
8 teach physicians, so individuals with a medical  
9 degree would be expected to have knowledge of the  
10 material that I teach.

11 Q. (By Mr. Knauss) Similarly with respect to  
12 Liquidia's definition, you do not personally meet  
13 the definition of a POSA offered by Liquidia that's  
14 recited on Page 9, correct?

15 A. Again, I do not have a medical degree in  
16 pulmonology or cardiology. I don't treat ILD  
17 patients, but I have relevant expertise that a POSA  
18 would be expected to have and that would be  
19 essential to understanding a patent.

20 Q. Right. So your testimony is that you have  
21 some expertise that is relevant to the expertise a  
22 POSA would have, but you do agree with me that you  
23 don't meet the definition of a POSA that is recited  
24 here, correct?

25 MR. BURROWBRIDGE: Objection, form.

1           A.       I do not possess all of the qualifications  
2           that are enumerated in these two statements, but I  
3           do have expertise that falls within the scope of  
4           what a POSA would have, I just don't have all of  
5           that expertise.

6           Q        (By Mr. Knauss) When you say falls within  
7           the scope, you mean have falls partially within the  
8           scope that you have some of the expertise but not  
9           all of it?

10          A.       Yes, that is right.

11          Q.        Okay. And I think we have established  
12          this but just to repeat, you have not treated an ILD  
13          patient, correct?

14          A.        Correct.

15          Q.        You have not treated a PH-ILD patient?

16          A.        That is also correct.

17          Q.        In fact, have you ever treated a patient  
18          in any clinical context?

19          A.        Aside from myself, no.

20          Q.        Do you have any prior training or  
21          experience with pulmonary hypertension as a disease?

22                  MR. BURROWBRIDGE: Objection, form.

23          A.        I am hesitating because over the course of  
24          my employment at the University of Chicago, I serve  
25          in a number of capacities, including as the

1           A.     I have not formed an opinion on that, but  
2     I rely on the experts in this case who I understand  
3     do consider CPFE to be included within the scope of  
4     PH-ILD. But that is not my opinion.

5           Q.     And what you have just referred to are  
6     things you have learned since working on this case,  
7     correct?

8           A.     Those specific beings we just talked about  
9     in the last question, yes.

10          Q.     Okay. And you have not talked to any  
11     other experts for UTC, the clinicians, Dr. Nathan or  
12     Wertheim for understanding of PH-ILD?

13          A.     I have not spoken with either Dr. Nathan  
14     or Dr. Wertheim.

15          Q.     Do you have any training or experience in  
16     WHO group classifications for PH?

17                 MR. BURROWBRIDGE: Objection, form.

18          A.     I know generally what they are.

19          Q.     (By Mr. Knauss) Did you know that before  
20     you started working on this case?

21          A.     I may have, I don't recall.

22          Q.     Do you have any training or experience in  
23     six-minute walk distance testing?

24                 MR. BURROWBRIDGE: Objection, form.

25          A.     That is a good question. Again, I am

1 measured a second time.

2 Q. It is not necessarily true that the ones  
3 who were not measured a second time would have  
4 performed more poorly?

5 MR. BURROWBRIDGE: Objection, form.

6 A. It is not a given that they would have  
7 performed more poorly and it is not a given that  
8 they wouldn't have, we just don't know. And that is  
9 the problem with heavily selected, trying to do  
10 statistical analysis on heavily selected patients.  
11 You don't know what to make of the results.

12 Q. (By Mr. Knauss) So in Paragraph 250 of  
13 your report, which is another area where you are  
14 discussing the same Faria-Urbina 2018 reference. In  
15 the middle of the paragraph referring to exclusions,  
16 you said, "These exclusions eliminated at least  
17 26" -- as you have corrected it -- "patients who  
18 would be expected to have worse functional outcomes  
19 than the 22 follow-up patients."

20 Do you see that?

21 A. I do.

22 Q. Okay. Your opinion is that even though  
23 there is no data on this, you would expect that  
24 those excluded patients would have performed more  
25 poorly in the six-minute walk test than the ones who

1 were included?

2 A. Yes.

3 Q. Aren't you speculating about that?

4 MR. BURROWBRIDGE: Objection, form.

5 A. I suppose you could say it is a  
6 speculation that if you are hospitalized due to  
7 unstable lung disease that it would be speculation.  
8 Well, you will do just as well in a six-minute walk  
9 distance despite the fact that your lung disease is  
10 so unstable it needed hospitalization or that you  
11 had a need for a lung transplant.

12 Patients who need lung transplants aren't  
13 doing very well. And so presumably they couldn't do  
14 as well on a six-minute walk distance.

15 Having to add other drugs because the drug  
16 wasn't working well enough suggests that those  
17 patients weren't doing as well. And so there is no  
18 data on it, but those reasons for exclusion suggests  
19 that they wouldn't have done as well had they  
20 actually been measured.

21 Q. (By Mr. Knauss) That is your opinion, even  
22 though you have never treated a PH-ILD patient,  
23 correct?

24 A. Correct.

25 Q. Never performed a six-minute walk test?

1 A. Correct.

2 Q. Never decided whether a patient was well  
3 enough to perform that test or not?

4 MR. BURROWBRIDGE: Object to form.

5 A. Correct.

6 Q. (By Mr. Knauss) And you did you talk to  
7 Dr. Nathan about this opinion?

8 MR. BURROWBRIDGE: Objection, form.

9 A. I did not talk with Dr. Nathan at all.

10 Q. (By Mr. Knauss) If you go back to one  
11 paragraph to 249 in the preceding page.

12 A. Uh-huh.

13 Q. Regarding Faria-Urbina 2018 you wrote,  
14 "Dr. Waxman was a strong advocate of his  
15 hypothesis."

16 Do you see that?

17 A. Yes.

18 Q. Do you question the integrity of  
19 Dr. Waxman's belief in his hypothesis?

20 A. Not in the slightest.

21 Q. Do you believe that he lacked the  
22 sufficient basis to have his belief?

23 MR. BURROWBRIDGE: Objection, form.

24 A. I have no basis for understanding what his  
25 basis was or his beliefs.

1           A.       The POSA would not have been able to  
2       consider that in assessing obviousness as of the  
3       priority date.

4           Q       (By Mr. Knauss) Take a look for me, please,  
5       at Paragraph 178 of your rebuttal report. That is  
6       in the Agarwal 2015 reference.

7           A.       (Witness complies.)

8           Q.       So you are noting there that the authors  
9       concluded in their abstract which was published as  
10      Agarwal 2015, that the, "Group 3 PH can be  
11      effectively," and then you have an ellipsis,  
12      "treated with inhaled treprostinil."

13                   Do you see that?

14           A.       Yes.

15           Q.       You don't dispute, of course, the  
16      expressed teachings of Agarwal, the paper does say  
17      that, correct?

18           A.       It says that -- the paper -- I have  
19      accurately quoted and you have accurately stated  
20      back to me what the paper says in the conclusion.

21                   The -- I would dispute the fact that the  
22      data in the paper indicate that treprostinil is  
23      effective. When they talk about effectively  
24      treating they don't say specifically effectively  
25      treating for one purpose but not effective for other

1 purposes.

2 Q. And so that is my next question. Your  
3 opinion is that you disagree with the authors'  
4 efficacy conclusion, correct? That is what you  
5 wrote in Paragraph 178.

6 MR. BURROWBRIDGE: Object to the form.

7 A. Yes, I disagree with the authors'  
8 efficacy.

9 Q (By Mr. Knauss) And the authors of Agarwal  
10 include Dr. Waxman, correct?

11 A. He is the only other author besides  
12 Agarwal.

13 Q. And he is an expert in PH-ILD, correct?

14 A. Yes.

15 Q. And you're not?

16 A. That is right.

17 Q. And you disagree with his stated  
18 conclusion, correct?

19 A. I disagree that the data he presents  
20 support the conclusions that he drew.

21 Q. You just think he is wrong?

22 MR. BURROWBRIDGE: Objection, form.

23 A. I believe the data in the paper don't  
24 support the efficacy conclusion he drew.

25 Q (By Mr. Knauss) And your opinion is that a

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C E R T I F I C A T E

I do hereby certify that I am a Notary Public in good standing, that the aforesaid testimony was taken before me, pursuant to notice, at the time and place indicated; that said deponent was by me duly sworn to tell the truth, the whole truth, and nothing but the truth; that the testimony of said deponent was correctly recorded in machine shorthand by me and thereafter transcribed under my supervision with computer-aided transcription; that the deposition is a true and correct record of the testimony given by the witness; and that I am neither of counsel nor kin to any party in said action, nor interested in the outcome thereof.

WITNESS my hand and official seal this 19th day of March,

*Paul Baca*

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Notary Public